# ANNALS of ALLERGY

*Published by the*

*American College of Allergists*

VOLUME 1

July through December, 1943

JAN 29 1944

# ANNALS of ALLERGY

PUBLISHED BY THE AMERICAN COLLEGE OF ALLERGISTS

Medical Library

Medical Library

July-August
1943

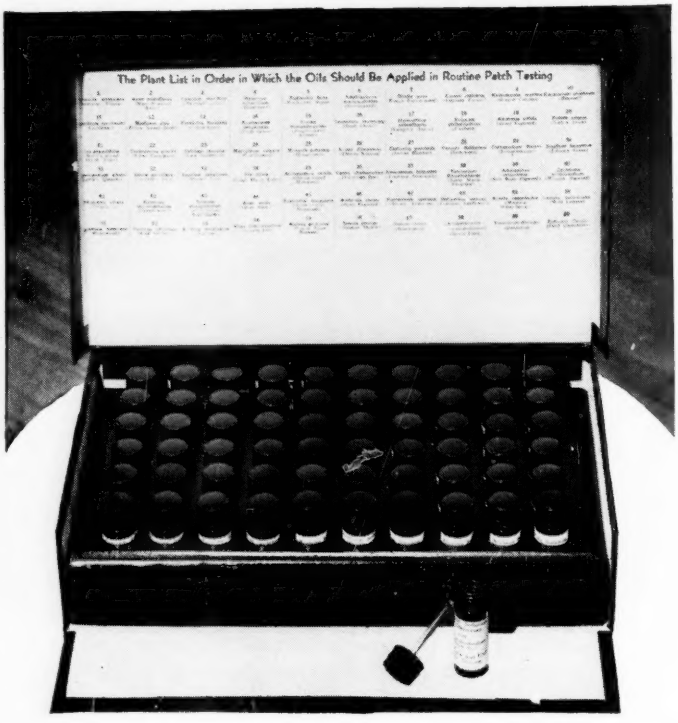
Volume 1, Number 1

Published Bimonthly

ANNUAL SUBSCRIPTION $6.00

SINGLE COPIES $1.50

# Plant Oleoresins
## *for PATCH TESTING*




We have sufficient data on distribution of wild vegetation throughout the United States, to supply a testing series of 60 of the most common and widely distributed weeds and grasses indigenous to any state in the Union.

Each vial contains sufficient material to make 100 (or more) patch tests. We have testing extracts six years old still potent.

## Graham Laboratories

*A Personal Service to the Physician in Diagnosis and Treatment of Plant Dermatitis*

WILLOW LANE—ROUTE 7 DALLAS 9, TEXAS

ANNALS of ALLERGY

Published by the American College of Allergists

Volume 1 July-August, 1943 Number 1

# ARMY ALLERGY

## REPORT ON ALLERGY CLINICS IN THE FOURTH SERVICE COMMAND

COLONEL SANFORD W. FRENCH, M.C. (USA)
MAJOR LAWRENCE J. HALPIN, M.C. (AUS)

ATLANTA, GEORGIA

IN World War I, little attention, professionally and statistically, was paid to allergic manifestations. The importance of the allergic diseases has been recognized by the present Medical Department. Today, allergy is a real problem in the army. Many skilled and trained military allergists are in a much better position to extend adequate care and sensible disposition to the allergic soldiers who have gained entrance into the ranks in spite of disqualifying regulations. It is inevitable that many applicants will be rejected who should be retained in service and many will be inducted who should be discharged.

Because of the lack of uniformity signified by Selective Service boards and the average station or general hospital, the percentage of allergic personnel in the modern army will closely parallel the ten per cent seen in civilian practice. The existing regulations for commissioned or enlisted service are essentially and basically similar. Four paragraphs of Mobilization Regulations 1-9 are devoted to seasonal hay fever and bronchial asthma. Mild hay fever is classified as acceptable for 1-A; moderate hay fever for 1-B, and severe hay fever is disqualifying. Any form of bronchial asthma is considered sufficient grounds for disqualification.[1] We agree that these regulations are justified and should be enforced; however, the possibilities of opinion differences are outstanding. The differentiation between mild, moderate and severe seasonal hay fever is extremely difficult even by the experienced allergist. If an applicant desires military service, his seasonal hay fever is mild or moderate; if he prefers civilian life, his symptoms are severe and disabling. And except during a pollen season, who can prove his statement wrong? The evident need for well, able-

bodied men has made it inevitable that many mistakes of induction and rejection should occur. Our interest has been consumed by the professional care and therapy extended to these allergic soldiers whether their symptoms were noted prior or subsequent to induction.

In past years, the correct diagnosis and adequate treatment of the allergic diseases in the army had been left to the interest and discretion of the individual medical officer at a single isolated station. During peace, the number of patients was somewhat limited, but even in those times, sufficient clinical allergy was encountered to warrant the continuation of such clinics at these stations.

In November 1941, the preparation of allergenic extracts by the Army Medical School in Washington, D. C., was discontinued. This move was necessary, not because of the suspected unimportance of army allergy, but because of the need for laboratory space required in the preparation of typhoid vaccine and other essential material possessing a higher priority. The knowledge of relief and savings in manpower days and hospitalization that can be accomplished through correct care and therapy led to the desire to coördinate and standardize the basis of management of the allergic soldier.

In March, 1942, the Allergy Section of the Surgeon's Office, Fourth Corps Area, was established. It was to be the purpose of this section to:

1. Establish and maintain an allergy clinic at each station hospital in this command.

2. Prepare, standardize and issue allergenic extracts.

3. Supervise the clinical investigation and therapy of the allergic diseases.

4. Register opinions on the physical examinations of officers and officer candidates who present allergic histories or findings at the time of their examinations.

5. Coördinate and submit reports on the allergic diseases in this command.

It was necessary that the methods of diagnosis, interpretation of findings and procedures of therapy be placed upon specific standards. In this way, the various individual clinics have operated as a unit under centralized control. As the first step in establishing clinics in each station hospital, a short, intensive course of instruction was given to the officers assigned to this service. Seventeen officers were in attendance. Of the 17, only one officer had had experience in the care of allergic patients, while the remaining 16 were unacquainted with any definite measures of investigation and therapy. It was not our intention to produce finished allergists as a result of this course of instruction. The success of this service depended upon arousing an interest in this specialty as well as impressing these officers with its importance in the army. A common

foundation for the investigation and treatment of these allergic army patients was established. The basis for management is readily manifested when a few factors are considered:

1. It has not been necessary to interrupt treatment of any patient who is transferred from one station to another within this command.

2. The manner of investigation, the interpretation of test reactions and the administration of therapy have been placed upon a simplified standard basis.

3. A patient remaining in this command faces no necessity for re-examination with each change of station. Should that same patient be transferred to a station outside the limits of this command, not only would re-examination be required, but any therapy would be discontinued because of the lack of necessary extracts.

By using extracts standardized on a basis with which all officers were acquainted, it was possible to correlate and further the efficiency of this group of clinics. The facilities of the Fourth Service Command Laboratory at Fort McPherson, Georgia, have been used for the extraction and standardization of all material used for diagnosis and treatment. This "central" laboratory for the supply of allergenic material has been one of the main factors assuring the success of this Allergy Service. The laboratory space required and the necessary technical assistance have interfered in no way with the daily routine duties of the laboratory staff.

The ultimate success of these clinics was partially dependent upon the simplicity and efficiency with which the basic necessary allergenic extracts were supplied for use by the inexperienced clinic officer. Because of the season of the year in which this Allergy Service was established (March) and because the tree pollen season in this general area has ended by May, it was decided to forgo for 1942 the use of tree pollen extract. On the accepted theory that timothy pollen contains an antigen common to all grasses, the purchase of this one pollen for extraction simplified the investigation and treatment of all grass sensitive patients. Ninety-five per cent of all fall hay fever and asthma symptoms are due to a ragweed sensitivity. The purchase of short and giant ragweed for extraction adequately supplied material for testing and treating the greater majority of these patients. Carelessweed (Amaranthus palmeri) was added to this compact list. The purchase of dry pollens for extraction was completed in the following amounts:

| | | |
|---|---|---|
| Short and giant ragweed pollen | 900 grams @ 9c = | $ 81.00 |
| Timothy pollen | 600 grams @ 14c = | 84.00 |
| Carelessweed (A. palmeri) pollen | 220 grams @ 50c (less 25%) = | 82.50 |
| Total cost | | $247.50 |

This total expenditure accounted for the entire supply of pollen material for extraction. At the same time, a supply of purified protein extract of inhalent material was purchased for extraction:

| | | | |
|---|---|---|---|
| Chicken feathers | 6 grams @ | $4.00 | $24.00 |
| Duck feathers | 6 grams @ | 4.00 | 24.00 |
| Goose feathers | 6 grams @ | 4.00 | 24.00 |
| Cat dander | 6 grams @ | 4.00 | 24.00 |
| Dog dander | 6 grams @ | 4.25 | 25.50 |
| Horse dander | 6 grams @ | 4.00 | 24.00 |
| Rabbit dander | 6 grams @ | 4.00 | 24.00 |
| Sheep dander | 6 grams @ | 4.00 | 24.00 |
| Orris root | 6 grams @ | 3.25 | 19.50 |
| Kapok | 6 grams @ | 4.50 | 27.00 |
| Cottonseed | 5 grams @ | 2.50 | 12.50 |
| Total cost | | | $252.50 |

In addition to these substances, a supply of dust was obtained at no cost.

All extraction was first completed in a three per cent (by weight) solution and sterilized by Seitz filtration. Subsequent standardization was based upon the nitrogen content of each extract. In this way, extracts of constant potency were assured each clinic at all times. Uniformity of clinical findings and results could be based only upon extracts of such proven standard strength. In 1942, 60 grams of ragweed, 15 grams of timothy and 15 grams of carelessweed pollen were extracted and standardized. Table I compares the original nitrogen content of each pollen extract with the standardized strength and the amount.

TABLE I.

| | Original Strength mgm N/ml | Clinical Strength mgm N/ml | Amount Standardized Extract |
|---|---|---|---|
| Ragweed | 0.4 | 0.1 | 3,680 mls. |
| Timothy | 0.2 | 0.1 | 3,726 mls. |
| Carelessweed | 0.24 | 0.1 | 2,208 mls. |
| Total | | | 9,614 mls. |

The inhalent extracts, other than pollens, were prepared for extraction and standardization in the same manner. To insure the sterility of each individual extract prepared for use in these allergy clinics, cultures and platings were determined for three successive days. Table II demonstrates the original nitrogen strength and nitrogen content of these extracts as supplied to the various clinics.

The allergy clinics of the Fourth Service Command have been supplied with extracts sufficient for all diagnostic and therapeutic purposes. The exact financial expenditure has been minimal. Considering the purchase

price of the materials extracted in 1942, it can be stated that $5.40 was expended for ragweed pollen, $2.10 for timothy, and $5.62 for careless-weed. The cost of the inhalent material extracted and sent to the allergy clinics can be estimated at $8.40. All clinics, therefore, were supplied with extract in adequate amounts for all diagnostic and therapeutic work for the amazingly low sum of $21.52. Though these computations do not

TABLE II.

| | Original Strength mgm N/ml | Clinical Strength mgm N/ml |
|---|---|---|
| Chicken feathers | 2.00 | 0.1 |
| Duck feathers | 0.8 | 0.1 |
| Goose feathers | 1.65 | 0.1 |
| Sheep dander | 2.45 | 0.1 |
| Dog dander | 1.80 | 0.001 |
| Rabbit dander | 2.00 | 0.001 |
| Cat dander | 1.14 | 0.001 |
| Kapok | 0.93 | 0.001 |
| Horse dander | 1.00 | 0.001 |
| Orris root | 0.35 | 0.001 |
| Cottonseed | 0.52 | 0.001 |

take into consideration the cost of laboratory personnel and maintenance, the amount saved by the preparation of the extracts in a central laboratory is surely considerable. A similar supply of extract purchased commercially would have resulted in an expenditure of several thousands of dollars.

During the twelve months in which this service has been in operation, new clinics have been added with the activation of each new camp. An attempt has been made to assign officers experienced in this specialty to these new stations, and in some instances this has been successful. In January, 1943, another short course was offered. This was necessitated by the personnel changes that had occurred during the past few months. The Allergy Service, as a result of this recent course, now embraces several stations of the Air Corps Medical Department. As originally instituted, the clinics were in operation only in those hospitals directly under the command of this office. With the change in organization in 1942, general hospitals in this area were added to this list of clinics. The addition of twenty-six Air Corps allergy clinics swells the total number now in operation to fifty-nine. All of these fifty-nine clinics are now being supplied

with diagnostic and therapeutic extracts from the original material purchased in 1942. In addition, standardized extracts have been furnished for the installation of approximately fifty clinics in Air Corps hospitals other than those in the states of the Fourth Service Command. Our problem of supply has been adequately met in this manner.

The question of trained personnel was a consideration of major importance; however, we feel that this has been overcome by these courses of instruction and the standard procedures that are in use in all of these clinics. The usual allergy clinic is held at intervals of twice weekly, though several stations have found it necessary to hold daily clinic hours. In the majority of instances, each officer in charge of the allergy clinic has been assigned additional duties. The application of only a few hours a week has extended much relief to many patients. At most station hospitals, these officers maintain wards to which allergy patients are admitted. In this way, the period of hospitalization for these patients has been decreased. Not only are these patients under the direct care of an officer interested chiefly in allergy, but investigation and specific therapy can be instituted immediately on the patient's entrance to the hospital. It has been stated by one officer in charge of a ward devoted exclusively to allergy, that his object has been to "keep it empty rather than filled" with patients. This is admittedly easier when that officer has had experience in the management of allergic patients. It should be emphasized that advanced training is not an absolute necessity, though it is desirable, in the operation of an allergy clinic or ward. Only fourteen officers in the fifty-nine clinics have had previous training in allergy. The training and experience of the remaining forty-five have been limited to our short courses and to the allergy work they have done since coming on active duty.

There has been established the important function of liaison between the allergy clinic and army examining board at most stations. This is extremely important, and in most instances, has been a large factor in determining the allergic status of an applicant prior to induction. Rejection or acceptance for general or limited duty is based upon a history and allergy investigation rather than a statement of the applicant as it might apply to existing regulations. This procedure will result in a greater percentage of accurate rejections and the acceptance of those whose type and severity of symptoms are amenable to therapy and compatible with military service.

A report of the work done in the allergy clinics of the Fourth Service Command was made to the Office of the Surgeon General. The material for this report was gained from twenty-one clinics in operation from April to October, 1942. The clinics not considered in this report had been established for an insufficient length of time to warrant including their findings. A report in the near future will summarize all clinics in active operation since the institution of this service.

The twenty-one clinics reported a total of 3,917 patients (Table III).

Of this number, 3,419 (88 per cent) were military personnel, and 498 (12 per cent) were of civilian status. At most stations, civilian dependents were extended the benefits of the allergy clinics, but several stations have limited their service to military personnel. The percentage of allergic patients per camp remained quite constant. Variation in the actual clinic census per day was dependent upon the size and geographical location of each station. As has been stated, it was necessary that the method of investigation and therapy of these allergic patients be placed upon a standard which would serve as an accurate guide to each medical officer and at the same time produce results that were statistically significant.

Pollen extracts in four dilutions were supplied each clinic. Titration of a patient's skin sensitivity was accomplished by intracutaneous testing with the weakest dilution (0.0001 mg N/ml) using Coca solution as a control. Production of a pseudopod wheal was accepted as evidence of a positive reaction at that test site. A positive reaction to this initial dilution classified this patient as an "A" sensitivity. If no reaction was noted, the next dilution (0.001 mg N/ml) producing a positive reaction designated a "B" sensitivity. A negative test to these, but a positive reaction to the next dilution (0.01 mg N/ml) determined a "C" sensitive patient. A "D" sensitivity was diagnosed in that patient who gave negative reactions to the above three dilutions, but reacted positively to the strongest dilution (0.1 mg N/ml). This titration permitted the specific sensitivity to be determined, as well as the degree of sensitivity to be classified. Treatment schedules for each pollen sensitivity were dependent upon the degree of sensitivity determined by this titration.

The remaining inhalent extracts were supplied to each clinic in the dilution (Table II) satisfactory for clinical intracutaneous use. In some instances, further dilution was advised. This was particularly true in the use of the cottonseed and feather extracts. Titration of skin sensitivity was also used in testing with dust extracts. Dosage schedules for pollen therapy have been prepared with a good degree of conservatism. For purposes of presentation and discussion, the cases seen in these 21 clinics are best classified as: seasonal hay fever; bronchial asthma, seasonal and perennial; perennial allergic rhinitis; and miscellaneous.

### SEASONAL HAY FEVER

Particular attention has been directed at the respiratory cases of allergy. This has been true for several reasons, the chief of which being the frequency with which these patients were seen. A total of 1,269 patients was classified as uncomplicated seasonal hay fever. Of these pollen sensitive patients, 633 were of ragweed origin, while only 150 were of the grass type. There were 486 cases of seasonal hay fever that presented histories and findings suggestive of both grass and ragweed sensitivity.

Complete histories and physical examinations were recorded in each instance. In the greater majority of these patients, the diagnosis of seasonal hay fever was determined by the history, and the titration of skin

TABLE III

| Post or Camp | Total Cases | | Pollen Hay Fever | | | X* | Pollen Asthma | | | Per. Br. Asthma | | Mixed S.H.F. and Br. Asthma | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Army | Civ. | Rag. | Grass | Mix | | Rag. | Grass | Mix | with Seas. | without Seas. | Rag. | Grass | Mix |
| A | 20 | 1 | 2 | 2 | 3 | 2 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| B | 380 | 89 | 44 | 14 | 56 | 1 | 19 | 5 | 14 | 33 | 89 | No statistics | | |
| C | 350 | 11 | 55 | 8 | 35 | 25 | 12 | 2 | 9 | 23 | 79 | 0 | 0 | 4 |
| D | 942 | 236 | 278 | 94 | 76 | 12 | 48 | 19 | 23 | 12 | 19 | 34 | 15 | 12 |
| E | 160 | 6 | 45 | 5 | 17 | 0 | 1 | 0 | 1 | 3 | 29 | 2 | 0 | 5 |
| F | 69 | 15 | 12 | 1 | 10 | 1 | 7 | 1 | 4 | 10 | 16 | 6 | 0 | 5 |
| G | 181 | 12 | 12 | 4 | 56 | 5 | 2 | 0 | 31 | 18 | 3 | 0 | 0 | 24 |
| H | 64 | 3 | 35 | 1 | 11 | 4 | 1 | 1 | 0 | 2 | 12 | 2 | 0 | 0 |
| I | 31 | 0 | 14 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 11 | 0 | 0 | 0 |
| J | 223 | 51 | 41 | 2 | 31 | 2 | 7 | 2 | 4 | 15 | 43 | 3 | 0 | 8 |
| K | 129 | 2 | 18 | 4 | 29 | 3 | 5 | 2 | 8 | 8 | 21 | 1 | 0 | 2 |
| L | 60 | 28 | 19 | 0 | 11 | 6 | 2 | 0 | 4 | 6 | 10 | 1 | 0 | 11 |
| M | 33 | 7 | 6 | 3 | 1 | 1 | 1 | 0 | 0 | 1 | 6 | 1 | 0 | 0 |
| N | 31 | 13 | 1 | 1 | 14 | 1 | 0 | 0 | 0 | 1 | 7 | 0 | 0 | 0 |
| O | 151 | 10 | 28 | 2 | 12 | 6 | 2 | 0 | 7 | 18 | 68 | 4 | 0 | 6 |
| P | 5 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 3 | 0 | 0 | 0 | 0 | 0 |
| Q | 331 | 0 | 7 | 4 | 40 | 15 | 0 | 1 | 2 | 13 | 118 | 0 | 1 | 4 |
| R | 79 | 10 | 3 | 4 | 34 | 13 | 0 | 1 | 13 | 15 | 14 | 5 | 3 | 10 |
| S | 74 | 0 | 2 | 0 | 5 | 3 | 0 | 0 | 6 | 6 | 10 | 0 | 0 | 18 |
| T | 31 | 0 | 3 | 0 | 16 | 7 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 |
| U | 75 | 4 | 8 | 1 | 27 | 3 | 1 | 0 | 11 | 3 | 17 | 0 | 1 | 1 |
| Total | 3419 | 498 | 633 | 150 | 486 | | 109 | 34 | 140 | 187 | 572 | 59 | 20 | 113 |
| | 3917 | | 1269 | | | 112 | 283 | | | 759 | | 192 | | |

test reaction classified the degree of sensitivity for subsequent pollen therapy. Most of the hay fever patients dated the original onset of their complaints many years prior to their induction into the army. A few, however, denied any previous complaints of this character. If the patient was seen sufficiently early the pre-seasonal method of therapy was employed. Co-seasonal therapy was instituted in many cases, as a great number of patients postponed their original visit to the allergy clinic until the onset of their symptoms.

TABLE III.—*Continued*

| Perennial Allergic Rhinitis | Misc.** | Constitutional Reaction | Hospital Cases | | | Aver. Hosp. Days | Total C.D.D. Cases | | | Cases Reclass. |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | S.H.F. | Asthma | Other Cause | | S.F.H. | Asthma | Other Cause | |
| 1 | 1 | 0 | 1 | 2 | 0 | 21.6 | 0 | 0 | 0 | 0 |
| 211 | 355 | 0 | 9 | 90 | 47 | 11.4 | 0 | 23 | 0 | No statistics |
| 29 | 96 | 3 | 16 | 158 | 36 | 20.25 | 1 | 26 | 1 | 48 |
| 249 | 381 | 24 | 5 | 55 | 24 | 21.9 | 3 | 19 | 1 | 42 |
| 8 | 27 | 1 | 1 | 14 | 0 | 10.7 | 0 | 10 | 0 | 21 |
| 8 | 13 | 0 | 1 | 8 | 4 | 18.7 | 0 | 2 | 1 | 1 |
| 27 | 46 | 3 | 6 | 35 | 9 | 19.1 | 0 | 7 | 0 | 19 |
| 6 | 13 | 0 | 5 | 40 | 0 | 23.7 | 0 | 5 | 0 | 13 |
| 0 | 4 | 0 | 1 | 8 | 1 | 17 | 0 | 0 | 0 | 6 |
| 84 | 21 | 2 | 4 | 86 | 34 | 22.7 | 0 | 15 | 0 | 35 |
| 1 | 22 | 0 | 1 | 21 | 0 | 18.3 | 0 | 5 | 0 | 0 |
| 13 | 6 | 0 | 4 | 10 | 5 | 5.6 | 0 | 5 | 0 | 4 |
| 5 | 16 | 1 | 0 | 8 | 4 | 21 | 0 | 3 | 0 | 0 |
| 10 | 25 | 2 | 0 | 11 | 12 | 11.8 | 0 | 1 | 0 | 0 |
| 21 | 25 | 0 | 5 | 57 | 11 | 23.6 | 2 | 5 | 0 | 24 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 69 | 62 | 1 | 1 | 153 | 62 | 10 | 0 | 31 | 0 | 21 |
| 9 | 24 | 1 | 2 | 22 | 7 | 11 | 0 | 2 | 0 | 14 |
| 9 | 17 | 0 | 3 | 34 | 12 | 10.5 | 0 | 0 | 0 | 16 |
| 6 | 2 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| 4 | 5 | 0 | 0 | 8 | 0 | 45.2 | 1 | 25 | 1 | 3 |
| | | | 65 | 820 | 268 | | 7 | 184 | 4 | |
| 770 | 1161 | 39 | 1153 | | | 18.1 | 195 | | | 267 |

*Seasonal hay fever of unknown origin.
**Urticaria 350, Migraine 79, G-I Allergy 73, Eczema 138, Food allergy 521.

It was somewhat surprising to learn that only 112 (3 per cent) patients could be classified as having "seasonal hay fever of unknown origin." As is known, this classification is peculiar to a section of the Country in which the Fourth Service Command is a large part. An interesting point in this regard is that practically all of these patients were diagnosed by experienced allergists. This would indicate that the inexperienced allergy

officer failed to recognize the allergic history as a basis for the symptoms in view of negative skin test reactions. It is regretted that information is not available regarding the locality from which these patients entered the army. It may well be that our report for the year will reveal a greater number of these patients after they have had a longer degree of exposure to the unknown causative factors.

Sixty-five cases of seasonal hay fever were admitted to the hospital during the season of 1942. The discomfort and severity of symptoms in these patients were sufficient to interfere with the performance of their duties. The usual hospitalization period was short and the patients were discharged as soon as the severity of their symptoms had been controlled. Institution of pollen therapy and continuation of that therapy in the outpatient clinic permitted these patients to perform full duty throughout the rest of the season. Only seven patients presented symptoms sufficiently disabling to warrant a certificate of disability discharge. These discharges represent the entire year of 1942, so it is conceivable and likely that the seven were discharged prior to the institution of the allergy service in this command.

### SEASONAL BRONCHIAL ASTHMA

Under this heading are included all cases of uncomplicated seasonal bronchial asthma and all patients with combined seasonal hay fever and bronchial asthma. Two hundred and eighty-three (7 per cent) limited their symptoms of wheezing, cough and respiratory difficulty to definite pollen seasons and denied the presence of any nasal or ocular association. All of these 283 were pollen sensitive on skin testing, with 109 being of the ragweed type, thirty-four being only grass sensitive and 140 showing symptoms during both the grass and ragweed seasons. As a whole, preseasonal and co-seasonal therapy produced very satisfactory relief in these patients.

Unfortunately, the hospitalization and disposition information of bronchial asthma has not separated the seasonal from the perennial cases. It can be safely assumed, however, that by far the greater majority of the asthmatics admitted to the hospital and/or discharged from the army were of the perennial type.

One hundred and ninety-two (4.8 per cent) patients had histories diagnostic of both seasonal hay fever and bronchial asthma. Fifty-nine of these limited their symptoms to the ragweed season and twenty admitted complaints only during the grass season. One hundred and thirteen patients noted the onset of their nasal and bronchial symptoms during the grass season with an extension to the end of the ragweed season. As a general rule, the asthmatic symptoms were relieved by pollen therapy before the hay fever complaints had been abated. The small number in this general classification, as compared to the large numbers of uncomplicated seasonal hay fever and perennial asthma is somewhat difficult to explain. In the first comparison, the usual induction board has passed the uncom-

plicated seasonal hay fever and rejected its association with seasonal bronchial asthma. In the second comparison, considerable imagination is necessary to understand the rationale of inducting perennial asthmatics and rejecting candidates with only seasonal symptoms. Included also under this heading are 187 patients with perennial asthma in whom seasonal (pollen) variation was determined by history and testing.

The above paragraphs reveal that 1,931 patients (49 per cent) were pollen sensitive. Pre-seasonal and co-seasonal methods of therapy were used to extend relief to these patients. Though perennial therapy could have been instituted in some cases, the frequent exchange of patients in and out of the command made the former procedures the methods of choice. In spite of the increased possibility of constitutional reactions associated with seasonal therapy, only 39 such reactions were encountered. In the treatment of these 1,931 pollen sensitive patients, it can be estimated that 28,965 (15 per patient) pollen injections were given. This low number of constitutional reactions is an indication of the conservatism in dosage employed and the care with which these injections were given. The manner in which the individual patient was titrated as to degree of sensitivity is undoubtedly directly responsible for this therapeutic safety. The lone constitutional reaction reported by one clinic occurred in a class A sensitive patient as a result of the original skin test dosage. Extreme care and attention to each therapeutic dosage in that patient produced excellent results with no subsequent constitutional symptoms. This would have been impossible had the dosage not been kept very low by the knowledge of that patient's degree of sensitivity. In no instance was hospitalization necessary for any of these thirty-nine patients. There were no residual symptoms or complications noted in any case.

### PERENNIAL BRONCHIAL ASTHMA

The soldier with a history of perennial bronchial asthma presents a real problem in the army. The solution to this problem would have been the rejection of that applicant at the time of his appearance for original induction. In the months of April to October 1942, 759 patients (19 per cent) in this classification were seen in twenty-one clinics. As previously mentioned, 187 had further aggravation by pollen or seasonal variation. There were 572 of these perennial asthmatics who denied and failed to show clinical evidence of any seasonal variation of their complaints. It is granted that the severity and frequency of attacks in this particular type of asthma are extremely variable. Many of these patients presented histories of asthmatic symptoms extending back several years into civilian life. There were also those patients who denied any previous complaints prior to their entrance into the army. The majority of these patients had had no allergy investigation in civilian life, though they had been diagnosed as asthma many times. Some few cases were seen with a definite history of past attacks, but with an absence of symptoms at the time of

examination. For the most part, the usual patient presented himself with the typical signs and symptoms of bronchial asthma. Immediate and temporary relief was extended to these patients with the use of epinephrine 1-1000 or ephedrine preparations for oral administration. The severity of some symptoms warranted the admission of many patients to the hospital. A total of 820 asthmatic patients was admitted to the wards. This represented 71 per cent of the 1,153 allergic cases requiring hospital care and attention. This one consideration stresses the importance and disabling qualities of asthma in the army. Upon investigation, multiple sensitivity was the rule. Dust sensitivity was predominant among these patients. Specific therapy was instituted during hospitalization and continued after the soldier's return to duty.

Complete investigation was accomplished in all instances. Consultations with the departments of nose and throat, x-ray and internal medicine established or ruled out any complicating foci or contributing causes. The response to therapy, though not accurately recorded for each individual case, can be assumed to be less satisfactory in these perennial cases than in the seasonal ones. The concern of those familiar with the frequency with which these perennial asthmatics are admitted into the army is occupied not only in immediate therapy, but also in the eventual disposition.

### PERENNIAL ALLERGIC RHINITIS

In tabulating the number of cases in this classification, it was again seen that experience was a large factor in establishing the diagnosis. Seven hundred and seventy patients were recorded as having complaints of year around nasal congestion, watery to mucoid nasal discharge and sneezing. Five hundred and sixty-five of these patients were reported from four clinics where experienced allergists were stationed. The diagnosis in each of the 770 cases was based on a history dating the original onset many years prior to this clinic visit. No attempt has been made in this report to list the various causative factors for each patient, but feathers, dust and the various animal danders are the agents most frequently involved. Nasal smears for eosinophilia have proven a distinct diagnostic aid in all cases.

Therapy in most instances of allergic rhinitis has consisted of the removal, if possible, of the offending agents. Administration of dust extract has been a decided factor in providing relief to many army patients. As stated before, titration of the skin sensitivity followed by therapy on conservative, low dosage schedules has been the procedure of choice. This dust therapy is usually administered on a perennial basis, though the ultimate maintenance dosage is small. Discontinuation of this extract has been suggested in each case when the symptoms and general condition of the patients so warrant.

### MISCELLANEOUS

Urticaria has been a problem to many medical officers as well as a

source of great concern to the individual allergic soldier. Few cases in this classification are sufficiently severe as to be disabling, but the degree of discomfort and irritation is marked. A total of 350 patients (8 per cent) was studied in these allergy clinics, with the diagnosis of urticaria being established. The causative agents included known allergy to a single food or group of foods, drug administration in routine medication, foci of infection, and administration of vaccines, serum and the like in treatment and prophylaxis. As in civilian practice, chronic urticaria presented distinct difficulty in making an etiological diagnosis. The single acute attack of urticaria was usually well controlled by the usual measures.

Migraine headaches have been the source of complaint to seventy-nine patients (2 per cent) in the allergy clinics. The etiologic basis for true migraine rests upon dietary allergy in a large percentage of instances. For this reason, a thorough history and elimination diets are necessary for correct diagnosis and therapy. Attempts were made to provide these patients with relief by the utilization of all measures of prophylaxis and therapy.

Seventy-three cases (1.3 per cent) of gastrointestinal allergy revealed this classification to be about equal to that of migraine. The diagnosis in these cases was largely one of elimination. Complete studies by x-ray disclosed the absence of any gross pathological lesions.

Though the presence of eczema among the troops is not a source of great concern, in 138 cases (3 per cent) there was sufficient irritation to seek treatment in the allergy clinic. The severity and location of some of the skin complaints were sufficient to warrant hospitalization and local therapy. The chronicity of the lesions in the usual eczema patient was outstanding. The original onset in the average history was noted to be many years prior to army induction. In most cases, improvement under therapy was only of a temporary nature, but no interruption of routine general duty was disclosed.

Since the majority of symptoms in these allergy clinics have been respiratory in character, our attention has been directed at the inhalent factors. This does not imply that the subject of food allergy, nor those allergic complaints due to food, have been less emphasized. The soldier in the army with a major food allergy finds that a dietary routine is extremely hard to follow. It is next to impossible for an elimination diet to meet with any degree of success in the average army mess. For this reason, the severe cases were usually hospitalized until their dietary routine was sufficiently inclusive to permit them the freedom of company mess. Of the 521 cases of food allergy (13 per cent) that were reported, the greatest number of patients was seen in the clinics maintained by experienced allergists. The specific diagnosis of food allergy reported by the other clinics was insignificant by comparison. Recognition of the complaints on a basis of sensitivity to food seems to be based on experience and an awareness of such a diagnosis.

DISPOSITION OF PATIENTS

An army medical officer, upon seeing a clinic patient, must record the ultimate disposition of that soldier as one of three places: duty, quarters or hospital. Since the nature and severity of many allergic complaints are such that a return to duty or rest in quarters are not satisfactory, admission to the hospital is advised. Of the 1,153 hospital admissions, 820 (71 per cent) presented symptoms characteristic and diagnostic of bronchial asthma. Unfortunately our questionnaire failed to separate the seasonal from the perennial asthmatic hospital patients. Seasonal hay fever accounted for only 65 admissions, which may seem unreasonably high to the civilian practitioner. The remaining 268 hospital patients are classified as "other allergic cause" and consist of migraine, urticaria, angio-neurotic edema, gastro-intestinal allergy and eczema. Two posts, Camp T and Fort P, reported the hospitalization of no allergy cases. This can, no doubt, be explained by the recent activation of Camp T and the geographical location of Fort P. The individual number of admissions for bronchial asthma varied from two at Fort A (on the Gulf Coast) to 158 at Camp C and 153 at Camp Q. In the usual instance, the period of hospitalization was shortened by proper allergy management and the institution of indicated therapy. Upon being discharged from the hospital, the allergic soldier continued his specific therapy as an out-patient attendant at the allergy clinic.

An average of 18.1 hospital days per patient was recorded for these 1,153 hospitalized allergic patients. Bronchial asthma can surely be considered as the foremost cause for prolonging this average. Some of these patients were candidates for a certificate of disability discharge from their first hospital day. The fact that the total hospitalization period awaiting such discharge is included explains to a great degree this relatively high average. Perhaps because of this one factor, the duration of hospitalization has been about constant for each station regardless of the number of allergic patients admitted to the wards. In those station hospitals in which allergic patients have been admitted to an "allergy ward" the period of hospitalization has shown a marked decrease. This is due to the control of the immediate environment as well as the institution of adequate specific therapy at an early period.

Of the total 3,917 patients seen in the allergy clinics, only 195 (4.3 per cent) were discharged from the service because of the severity of their complaints and their resistance to specific therapy. Of those discharged, 184 were diagnosed as bronchial asthma, seven as seasonal hay fever and four as migraine, urticaria or angio-neurotic edema. Inasmuch as these certificates of disability discharge records are for the period of January to October, 1942, it is probable that some few of these may have been so discharged prior to the institution of this Allergy Service.

As a rule, most of the 184 asthmatics discharged were of the severe perennial type. Their discharge was based upon the severity of their

complaints, the amount of resulting disability and the continued aggravation of their complaints by military service. One interesting and important feature may be drawn from comparing the number of asthmatics given a certificate of disability discharge, with the total number of asthmatics reported by the individual station. At Fort D, only nineteen cases of asthma were discharged from the service; however, this same post reports a total of 182 cases of asthma seen in the allergy clinic. At Fort B, twenty-three asthmatic soldiers were given certificate of disability discharges, whereas more than 160 asthmatics were clinic patients. The same important comparison holds true at the smaller station hospitals. Fort L found it necessary to discharge five cases of bronchial asthma because of disability and at the same time reported thirty-six asthmatic patients on their clinical report. Camp R reported two asthmatic patients as being discharged from the service and yet reported fifty-eight cases of asthma in their clinical files. From these comparisons an estimation can be made as to the beneficial role played by the allergy service in the care of bronchial asthma in maintaining these patients on a duty status.

One of the most encouraging services offered by competent allergy clinics is that of extending relief to all eligible soldiers. The reclassification of the allergic soldier from general to limited service has been successfully managed and further completed by adequate allergy therapy. Prior to the institution of these allergy clinics, most cases of asthma were discharged from the service if their symptoms were apparently aggravated by their military duties. Two hundred and sixty-seven allergic patients (6.3 per cent) were successfully reclassified and retained in military service by correction or treatment of their allergic complaints. At the usual station, the number of allergic patients reclassified far outnumbered the total number of patients given a certificate of disability discharge. Three stations failed to reclassify any allergy patients. The total number of patients discharged on a certificate of disability from these three posts was only nine.

One of the most important features of military medicine is the effort to maintain effective duty in the personnel. The hospitalized soldier is as truly ineffective as one absent from duty for any other reason. The allergic soldier, correctly diagnosed and adequately treated, can be maintained at full duty in a far greater percentage than happened in World War I. If mobilization regulations were strictly and universally followed, there still would be a sufficient amount of clinical allergy in the present army to warrant the operation of allergy clinics. As it is, more applicants with allergic histories are being accepted into military service with each new demand on the Selective Service quotas. The evidence for this statement is based on the growth of the Allergy Service in the Fourth Service Command since its institution in 1942. It is our belief that regulations should not be changed to allow indiscriminate admission to military service of all allergic applicants. It is our contention, however, that

adequate investigation and therapy should be extended to those who are, and will be, in service under present regulations. Advancement in methods of diagnosis and progression in therapeutic measures have assured the allergist an important role in today's military medicine.

SUMMARY

1. An Allergy Section was established in the Fourth Corps Area as of March, 1942.

2. Preparation and extraction of all allergenic material used in these clinics have been accomplished at the Fourth Service Command Laboratory.

3. A total of $500 was expended to purchase supplies for extraction. The total cost of pollen extracted for 1942 was $13.12. Inhalent material extracted cost approximately $8.40. Thus, all clinics have been adequately supplied with allergenic extracts at a cost of $21.52, representing an over-all saving of several thousands of dollars.

4. In a summary of twenty-one clinics, 3,419 army allergy patients and 498 civilian allergy patients were reported to the Surgeon General's Office.

5. A total of fifty-nine allergy clinics has now been established in this command. Twenty-six of these are in operation at Air Corps station hospitals and thirty-three are functioning in Fourth Service Command hospitals.

6. From January to October, 1942, 1,153 allergy patients were admitted to the hospitals of these twenty-one stations. The average number of hospital days was 18.1.

7. There were 195 allergic patients given certificate of disability discharges, as compared to 267 who were successfully reclassified and maintained on limited service.

REFERENCE

1. Paragraphs 27, 28, 29 and 58 *e*, Class 4, M.R. 1-9, (Oct. 15) 1942.

---

**ALLERGY IN NORTHERN AFRICA**

*Major Myron A. Weitz* writes from Northern Africa some interesting observations: . . . "Yes, there is hay fever and asthma here. I have had some slides out, and in addition to grass, plantain and some pollens which I am unable to identify, I have seen alternaria and hormodendrum. Unfortunately, we are not set up to do any testing here, and about all I can do so far is give some supportive therapy. I have written home for some material and hope to get the opportunity to do a bit more than that. The patients whom I have seen with hay fever have all told me that their symptoms are considerably worse here than in the States. It is common for them all to say that the extreme dustiness and that very damp cool nights contribute to their respiratory difficulties. I think I am going to have a great deal of fun trying to find out what it's all about. I hope you will keep me informed on some of the new developments in the field."

# POSSIBLE ETIOLOGY OF APPENDICITIS

L. O. Dutton, M.D.
EL PASO, TEXAS

IN the past there has been much discussion on the subject of the allergic nature of certain abdominal complaints which simulated surgical conditions. It is believed that one can state as a categorical fact, without elaborate reference to the literature, that not only do those of us whose main interest is in allergy accept such a concept, but most others also recognize this as true. Certainly, in regard to pain in the right lower quadrant, one frequently sees patients presenting symptoms which can hardly be explained on any other than an allergic basis. Likewise, some of the patients present clinical pictures of such confusion that it is impossible to state whether there is a simple allergic pain or a true inflammation of the appendix and there is no recourse other than operation to insure safety for the patient.

This paper presents a clinico-pathologic concept of the disease appendicitis which accepts allergy as a fundamental etiologic factor that offers an explanation of much that is confusing, both to the clinician and to the pathologist.

At the outset, it should be understood that no opposition is offered to the well-established surgical treatment of the condition, but rather a rational explanation is sought for certain features of the clinical course and pathologic findings of appendicitis which have been puzzling in the past. Other etiologic factors no doubt exist and may well operate either in conjunction with allergy or independently of it.

From the clinical angle, the disease is not clear-cut. Most surgeons agree that there is chronic or recurrent appendicitis, as well as catarrhal and suppurative appendicitis, the latter two being either subacute or acute, and the last, of course, having a final stage of gangrene and perforation. Clinically, this picture of the condition is well enough until the abdomen is opened and the organ is inspected. Then it is found that there is little correlation between the clinical features and the gross appearance. One step further into the hands of the pathologist and the correlation between clinical features and observed changes in the organ breaks down almost completely. Even the clinicians, when they make critical studies of the disease, come out with the answer that an undetermined large percentage of patients are not significantly relieved of their complaints following surgical removal of the appendix.

There is undoubtedly some logical explanation for the almost total lack of correlation between the clinical and pathologic findings in operative cases, other than lack of perception of the surgeon or the pathologist. This aspect of the disease has been so freely discussed that it is almost a jest.

Finally, there is no generally accepted concept of the etiology of the disease. True, one says that obstruction and interference with emptying will cause inflammation and that foreign bodies, fecaliths, and parasites will result in damage to the organ. But one seldom finds parasites or foreign bodies in removed appendices, and only in a small percentage of cases are obvious anatomic obstructive lesions found. These remarks are not intended as detailed discussion of the subjects touched upon, but are only reminders that there is a definite need for a more clear-cut concept that will explain some or all of these confusing features.

There seems to exist ample reason for studying some of the problems connected with appendicitis. Some of these reasons are:

1. There is no acceptable theory regarding the etiology of this disease.
2. There is no uniformity of opinion regarding the pathology of the disease.
3. There is little correlation between the pathologic findings and the clinical course of the disease.
4. There is little assurance of operation relieving the symptoms which led to surgical interference.
5. Appendicitis remains extremely difficult to diagnose, except in its most definite and typical form.
6. There is no satisfactory explanation for the rather frequently occurring, but seldom commented-upon local eosinophilia.

There are others, but these are ample to indicate that there are still many things which we might learn concerning this disease, and that there is ample justification, at least for the consideration, of new viewpoints concerning it.

Before reviewing studies and drawing conclusions, it might be well to state the thesis which is to be supported, namely—that there is sufficient evidence to regard allergy as one of the prime etiologic factors in appendicitis, and that such a consideration clarifies many points in an otherwise very confusing situation. This thesis in no way refutes the position of the surgeon, nor does it classify appendicitis as a non-surgical disease. The purpose in presenting this thesis is to explain some differences of opinion and to seek a logical answer to the questions enumerated above.

My own concept of the disease has been formulated from a consideration of several aspects: first, a careful study of individual case histories which have developed under my personal observation; second, a statistical study, the third, the histopathologic evidence.

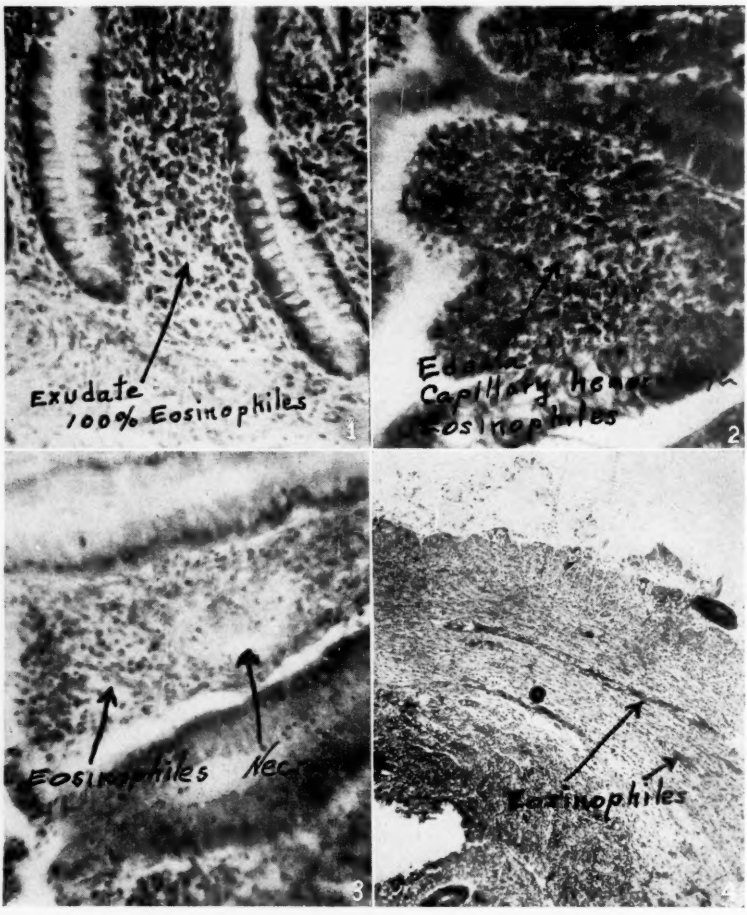
My interest in this problem arose many years ago when in many cases I was unable to correlate the pathologic findings with the clinical diagnosis made by surgeons for whose opinions I had the greatest respect. A little later I had the opportunity of observing rather intimately over a period of years several patients who were eventually subjected to appendectomy without the relief of symptoms, and in whom symptoms were postoper-

atively relieved by allergic management. With an increased interest in allergy, other patients were observed who, in the main, presented a story somewhat as follows: while under observation and treatment for definite allergic syndromes, such as hay fever, asthma, or urticaria, there would appear episodes of abdominal pain typical of appendicitis in location, and sometimes associated with nausea and vomiting. However, leukocytosis, fever, rigidity, were entirely lacking. Gastro-intestinal allergy was suspected and on occasions, these symptoms could be relieved with ephedrin or adrenalin. Occasionally, a small dose of narcotic would be required to relieve these symptoms. Generally, following the first of such episodes, it was only a matter of time until succeeding similar episodes would occur, and due to inability in some cases to find offending foods, or to indifference on the part of the patient in regard to diet, a varying number of such attacks occurred. Eventually, an attack would occur which presented, not only the above findings, but in addition, an attendant fever and leukocytosis. Operation was then advised, and on surgical removal, a definitely inflamed and pathologic appendix would be found. This course of events has been observed sufficiently often to outline it as a fairly characteristic clinical development of the disease.

To gain further insight into this problem, consecutive cases of appendicitis were studied. The study consisted of 123 consecutive cases with operation following a clinical diagnosis of appendicitis of some degree. Of these 123 cases, the clinical diagnosis was as follows: acute appendicitis, seventy-seven; subacute appendicitis, nineteen; chronic appendicitis, twenty-seven. The pathologic diagnosis on these appendices was as follows: acute diffuse, thirty-five; catarrhal appendix, thirty-eight; subacute appendix, five; chronic appendix, seventeen; fibrosed appendix, twenty-six; normal appendix, two. There seemed to be little correlation between symptoms and pathologic findings, as evidenced by the inability to differentiate clinically between the various pathologic types.

These appendices were studied grossly and microscopically in considerable detail and an effort was made to reconstruct the course of the pathologic change taking place. It is fairly apparent what happens when mechanical obstruction damages the organ. But without the presence of fecaliths, adhesions, or kinking, there is left only edema to account for obstruction. What causes this initial edema and damage? Mechanical obstruction admittedly occurs, due to fecaliths, kinks, or adhesive band on occasion, but functional obstruction due to edema is supposed to occur frequently. It is believed that this functional edema is primarily an allergic reaction. After a study of sections of many appendices, it appears that the pathologic condition observed is nowhere inconsistent with the changes that are known to occur in allergic reaction, and that up to a certain stage, these changes, which are edema, capillary congestion, and infiltration of eosinophiles, are entirely reversible and are similar to the tissue reaction seen in other locations due to allergy.

Thus it may be said that the fundamentals of the allergic response in




Figs. 1, 2, 3 and 4.

*(See legends on opposite page)*

the tissues consist of reversible edema, congestion, and cellular infiltration leading, in some instances, to irreversible necrosis and vascular changes. Of the cellular elements involved, the eosinophile is an important and striking feature.

Changes of this type are probably the most common seen in appendices. This impression has been gained over a number of years, following the examination of many hundreds of appendices, and has been crystallized by the careful appraisal of 125 consecutive cases and specimens encountered in a small hospital and all clinically diagnosed and removed by others than the writer. Of course, it is impossible to study the consecutive changes that take place in any given organ, as one can examine an ap-

**Legends for Figures 1-4**

Fig. 1. This case was diagnosed as acute appendicitis pre-operatively and post-operatively. There was pain in the right lower quadrant, but no nausea, no vomiting, and no fever. The total white count was 14,700 with 69 per cent polymorphonuclear cells, 12 per cent immature forms and one eosinophile. The patient had had attacks of appendiceal pain over a period of six years. There was no history of allergy. On examination, the appendix appeared edematous. There was no other gross abnormality. Microscopic examination revealed edema, and eosinophilic infiltration of the mucosa was the only pathologic finding. The figure illustrates this. This is an illustration of the early allergic-type edema.

Fig. 2. This case was diagnosed acute appendicitis pre-operatively and postoperatively. There was pain and nausea, but no fever and vomiting. The total white count was 9,400 with 71 per cent polymorphonuclear cells, 16 per cent immature forms, and 1 per cent eosinophiles. There was no allergic history. On examination the appendix was found to be congested and edematous, and the mucosa was marked with petechial hemorrhages. On microscopic examination, there was little or no change in the serosa muscularis and submucosa, while the mucosa was edematous and showed many areas of capillary hemorrhage with destruction of the normal architecture and a few spots of focal necrosis. There was no cellular infiltration whatever in any coat, except a large percentage of eosinophiles in the submucosa. Details of the capillary hemorrhages and edema with eosinophilic infiltration are clearly demonstrated.

This specimen represents a rather advanced stage of the so-called catarrhal appendix, except that there are no neutrophiles present. It probably represents an acute allergic reaction just before the stage of transition to a suppurative reaction.

Fig. 3. This case was diagnosed as subacute pre-operatively and postoperatively. There was pain in the right lower quadrant and fever, but no vomiting. The total white count was 8,100 with 65 per cent polymorphonuclear cells, 7 per cent immature forms, and 1 per cent eosinophiles. On examination, the appendix was markedly congested and there were numerous erosions of the mucosa. Microscopically, there was nothing present other than edema and eosinophilic infiltration, congestion and focal spots of necrosis.

Fig. 4. This case was diagnosed as acute appendicitis pre-operatively and post-operatively. There was pain in the right lower quadrant, but no nausea, no vomiting, and no fever. The total white count was 7,450 with 73 per cent polymorphonuclear cells, 20 per cent immature forms and 6 per cent eosinophiles. The patient suffered from hay fever and asthma over a period of years, and there was a known impressive list of foods which caused allergic reaction. On examination the appendix showed some fibrosis, but no other pathologic change other than numerous eosinophiles scattered throughout the entire wall.

---

pendix only at a single stage of the evolution of the disease. However, it is possible to reconstruct what is probably the sequence of events.

The first and simplest pathologic change which takes place in the appendix is edema. Many specimens are encountered which, on gross and microscopic examination, show no other deviation from the normal. Many such specimens are removed from patients who have the clinical symptomatology of acute appendicitis. These patients, however, regularly have blood pictures which are not characteristic of acute suppuration. We have encountered in our series many specimens illustrative of this type of appendix. Many of these have a very definite infiltration of eosinophiles into the mucosa, but diligent search fails to reveal any diffuse or focal infiltration of neutrophiles (Figs. 1-13).

Apparently the next step which occurs in the development of appendicitis is an engorgement of the blood vessels leading to petechial hemor-

Figs. 5, 6, 7 and 8.

*(See legends on opposite page)*

rhage. Along with this, there is generally seen edema of the serosa and submucosa with some edema of the muscularis. Many such specimens as this are seen which still fail to show neutrophilic infiltration. Such an appendix is illustrated. This picture, of course, conforms to the classical description of the acute catarrhal appendix except for the absence of neutrophiles. In such an appendix, after careful searching, sometimes of many sections, small focal areas of necrosis are found characterized by pyknosis, but still without any infiltration of neutrophiles. Such damage to the appendix, no doubt, paves the way for bacterial invasion, which, in turn, converts the microscopic appearance to a typical suppurative pic-

**Legends for Figures 5-8**

Figs. 5 and 6. This case was diagnosed chronic appendicitis pre-operatively and postoperatively. There was no pain, no vomiting, and no fever. The total white count was 8,300 with 69 per cent polymorphonuclear cells, 2 per cent immature forms, and 5 per cent eosinophiles. On examination the appendix was found to be edematous and congested and grossly appeared no different from many specimens which had been diagnosed acute appendicitis. Microscopically, there was no change other than eosinophilic infiltration in the mucosa and other coats, which in some instances amounted to almost eosinophilic abscess. There was edema and congestion. There were no neutrophiles present.

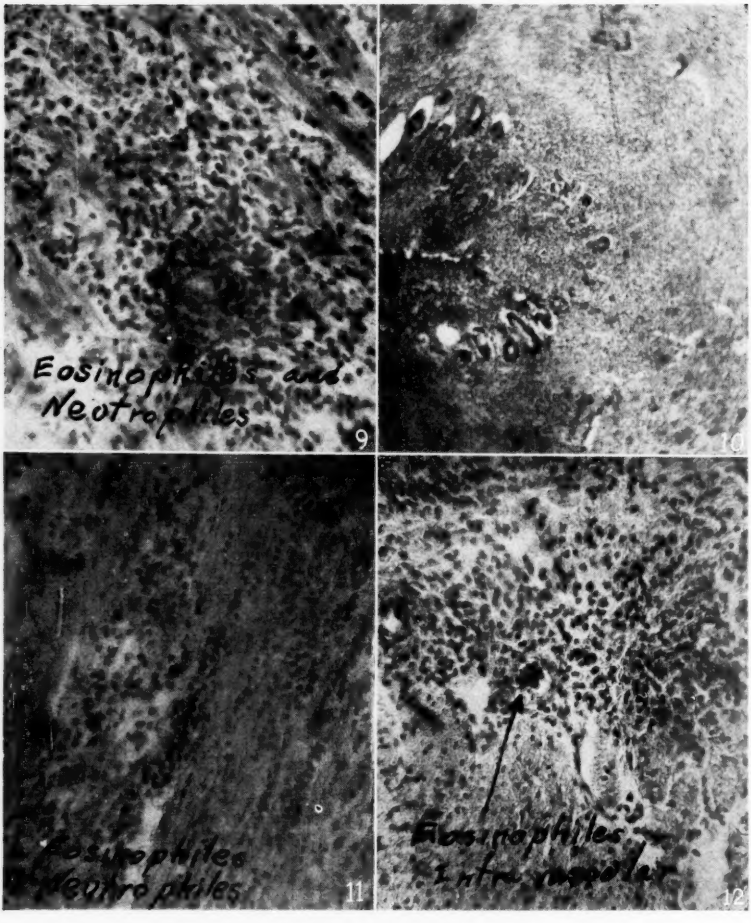
Figs. 7 and 8. This case was diagnosed acute appendicitis pre-operatively and postoperatively. There was acute abdominal pain and nausea, but no vomiting and no fever. The total white count was 11,200 with 78 per cent polymorphonuclear cells and 11 per cent immature forms, and no eosinophiles. The patient had had recurrent headaches and seasonal hay fever. Symptoms of appendicitis had persisted over a period of two years. On examination the appendix was found to be congested and edematous, but otherwise showed no change. On microscopic examination, the mucosa was seen to be edematous and heavily infiltrated with eosinophiles. The blood vessels were distended with blood. There was no neutrophilic infiltration at any point.

Figure 7 illustrates details of the mucosa while Figure 8 illustrates the congestion of the blood vessels of the serosa. This case probably illustrates an early catarrhal or allergic reaction still definitely in the reversible stage.

---

ture characterized by neutrophilic invasion, running the whole series of changes leading to gangrene and perforation. The first of these changes is reversible, and if the organ is not removed, interruption of the development of this classical picture allows the appendix to return to normal without any residual changes that can be recognized either grossly or microscopically. However, if the point of necrosis is reached with its attendant sequence of events, the changes become irreversible, and, if the organ is not removed and healing takes place, there are left recognizable changes in the nature of fibrosis.

Throughout these various stages, the behavior of eosinophiles is extremely interesting. They cease to be confined to the mucosa, migrate to the submucosa, muscularis, or serosa, and are found distributed either diffusely or perivascularly. A number of specimens have been encountered in which practically the entire component of invading cells is composed of eosinophiles. More often there is found a definite admixture of neutrophiles and eosinophiles in varying proportions until, finally, one sees what is apparently the complete suppression of the eosinophilic response by neutrophilic cells. One cannot help but be impressed by the fact that the eosinophile can and does take part in an inflammatory reaction, this many times being the most striking feature of the microscopic appearance (Figs. 1-13). Throughout a series, the various elements of these reactions—that is edema, congestion, eosinophilic infiltration, and so forth—are seen in various degrees, sometimes one, sometimes another being the more prominent.




Figs. 9, 10, 11 and 12.
*(See legends on opposite page)*

In an interpretation of these observations, it becomes apparent at once that we are without the information which might be gained from serial observation of a single appendix. It, therefore, becomes necessary to reconstruct these changes from observation at a given moment of a large number of specimens. One cannot be absolutely certain, then, whether these changes are static and represent different types of response to irritation, but interpreting them as different stages in a progressive process is much more logical and understandable. The similarity of the above picture to that described for other tissues as a result of allergic stimuli is

**Legends for Figures 9-12**

Fig. 9. This case was diagnosed acute appendicitis pre-operatively and post-operatively. There was pain in the right lower quadrant, but no nausea, no vomiting, and no fever. The total white count was 12,000 with 84 per cent polymorphonuclear cells, 19 per cent immature forms, and no eosinophiles. On examination, the appendix was found to be greatly edematous, the serosa being enormously thickened, while the muscularis, submucosa and mucosa did not seem to be involved in the edematous process. All these coats, however, showed numerous eosinophiles, while the serosa in its outer layer showed a few eosinophiles plus numerous neutrophiles. Figure 9 illustrates the details of the mixed cellular exudate in the serosa. This could be an illustration of marked allergic edema with superimposed infection, the process taking place in the serosa rather than in the mucosa.

Figs. 10, 11 and 12. This specimen is from a case diagnosed acute appendicitis, both pre-operatively and postoperatively. The patient had diffuse abdominal pain, nausea, and fever. The blood count was 20,000 total white with 82 per cent polymorphonuclear cells, 10 per cent immatures, and 3 per cent eosinophiles. There had been recurrent symptoms of appendicitis over a period of three years, and the patient suffered from seasonal hay fever. On pathologic examination, the appendix was definitely inflamed and thickened, with lumen containing pus. There was considerable destruction of the mucosa. Microscopically, all coats show a diffuse infiltration of polynuclear neutrophiles and numerous eosinophiles. In a few areas eosinophiles predominate.

Figure 10 shows the general character of infiltration. Figure 11 shows the collection of eosinophiles in the muscularis and the serosa.

Figure 12 shows a blood vessel containing a large percentage of eosinophiles before migration to the tissues. This case illustrates a far advanced inflammatory reaction of the suppurative type, having gone to an irreversible stage, in which there was probably an early allergic type reaction.

---

obvious, and although one must probably admit, as stated by Sulzberger, that there is no tissue response pathognomonic of allergy, it is certainly true that most of the allergic reactions which have been well observed conform in rather close detail to the picture just described. Likewise, most tissue responses of a non-allergic nature differ from this picture in certain essential details. Therefore, although a tissue response does not prove allergy, it certainly is strong presumptive evidence of an allergic reaction.

To throw further light on this problem, the blood counts which were done on these patients were studied with a view to further elucidating the problem. The details of this study have been presented elsewhere. In the main, conclusions drawn from these counts are that in acute diffuse appendicitis the total white count is almost invariably above 12,000 and the total polymorphonuclear per cent is above eighty. In the other groups of cases the figures for these items are, in the main, below these levels. There is no significant difference between the counts obtained in patients who had pathologically catarrhal, subacute, chronic, or fibrosed appendices, nor is there any consistently significant difference between these counts and those seen in patients with relatively minor digestive upsets. This last was found in spite of the fact that a large number of these patients presented a clinical picture diagnosed as acute appendicitis.

It would seem that if there were any relationship between allergy and appendicitis, one would expect to find a high incidence of allergy among those patients subjected to appendectomy. Such information proved to be difficult to obtain in a routine history generally secured by the hospital

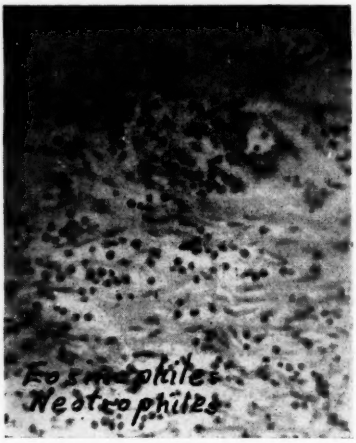



Fig. 13. This case was diagnosed acute appendicitis pre-operatively and post-operatively. There was pain in the right lower quadrant, nausea and vomiting, but no fever. Total white count was 13,000 with 87 per cent polymorphonuclear cells, three immatures, and no eosinophiles. The patient had many known food sensitizations and had had similar attacks for five years. Grossly the appendix was highly edematous and there was destruction of the mucosa and a cellular infiltration throughout all the coats. But this infiltration was composed of both eosinophiles and neutrophiles in about equal numbers. The illustration shows details of this exudate.

historian. In order that there would be no question of forcing a biased history, this portion of the study was made as simple as possible. Each patient was asked if there was any personal history of hay fever, asthma, or urticaria. There was no elaboration of these questions, and no other possible allergic condition was accepted as proof of allergy. Nor was family history accepted as proof of allergy. For various reasons, an allergic history was obtained on only eight-seven of these patients. It was found that forty-five of these eighty-seven patients had or had had definite hay fever, asthma, or urticaria. In view of the fact that the generally accepted incidence of these three allergic conditions in the general population is 10 per cent or below, it seems that the incidence obtained here, although admittedly based on too few cases to be statistically reliable, does indicate a definite trend which, upon further study, may be highly significant

In view of these considerations, it appears that allergy may explain some of the questions asked in the opening of this paper. A theory con-

*(Continued on Page 53)*

# DE-ALLERGIZATION VERSUS HYPOSENSITIZATION

ERICH URBACH, M.D., AND PHILIP M. GOTTLIEB, M.D.

PHILADELPHIA, PENNSYLVANIA

CAREFUL observers have not failed to note that progress in experimental approach to allergy and in diagnostic techniques has not been paralleled by advances in the therapeutic management of diseases of hypersensitiveness. Aside from prophylactic measures, such as elimination or avoidance of allergenic agents, the methods of hyposensitization are at present nearly exclusively employed. While they are sometimes quite effective, in many other cases the results are unsatisfactory and, above all, only temporary.

This is not too surprising in view of the fact that therapy based on the principles of hyposensitization does not actually alter the allergic pattern of the patient. Methods which would restore the hypersensitive organism to a normergic state of reactivity would constitute a major therapeutic achievement. Elsewhere[29] we have fully discussed the basic theoretic laws which led us to introduce the concept of de-allergization. Here we shall confine ourselves to a discussion of the experimental background and the clinical application of this new form of anti-allergic therapy.

## EXPERIMENTAL BASIS OF SPECIFIC HYPOSENSITIZATION (DESENSITIZATION)

The term hyposensitization (desensitization) designates the procedures in which the organism is given small quantities of antigen in repeated and increasing doses, with the result that the blood contains an excess of free circulating antibodies. This concept is based on the results of the following experiments. When allergized animals are treated with increasing amounts of antigen injected at intervals of several days, subsequent administration of a usually lethal dose will be tolerated without manifest symptoms, although the lungs (in the perfusion experiment) and the uterus (in the Schultz-Dale experiment) are still anaphylactic. In other words, they have a high antibody content. At the same time it is always possible to perform passive transfer with blood serum from the hypo-sensitized animals. Therefore the clinical insensitiveness can be explained only on the basis of an excess of free circulating antibodies (Table I).

So long as there is an excess of free antibodies in the blood, the individual does not give manifest responses to renewed administration of antigen: this may be explained on the grounds that the antigen is so completely neutralized in the blood that it cannot enter into an antigen-antibody reaction with the sessile antibodies in the tissues. This working hypothesis (Weil[32]) serves to explain how at a time of complete physical insensitiveness, there can be positive skin reactions to local (e.g., intradermal) administration of the allergen, and, above all, the fact that shortly

From the Allergy Service of the Jewish Hospital, Philadelphia.

TABLE I. SUMMARY OF MECHANISMS OF ANTI-ALLERGIC METHODS (URBACH)[28]

| State of Animal | Type of Protection | Effect of Shock Dose | Perfusion of Isolated Lung | Dale Test on Uterus | Passive Transfer |
|---|---|---|---|---|---|
| Nonallergized | — | — | — | — | — |
| Allergized | None | + | + | + | + |
| Allergized | Hyposensitization by increasing doses of antigen at intervals of more than two days | — | + | + | + |
| Allergized | De-allergization by massive doses of specific antigen, causing severe macroshocks | — | — | — | — |
| Allergized | De-allergization by injection of specific antigen, causing slight macroshocks; freedom from symptoms on subsequent massive doses of antigen | — | — | — | — |
| Allergized | De-allergization by preceding doses of specific antigen (skeptophylaxis), acting through microshocks — Intravenously | — | — | + | + |
| | De-allergization by preceding doses of specific antigen (skeptophylaxis), acting through microshocks — Orally | — | — | — | — |

after the administration of the antigen is stopped, the organism again appears clinically to be strongly hypersensitive. The reason for this is that in the absence of further antigen administration, the production of circulating antibodies ceases, so that antigen administered later will react directly with the cellular antibodies, thus causing allergic manifestations.

Correctly evaluating the mechanism of this procedure (temporary clinical insensitiveness, without cure), Cooke[6] and also Levine and Coca[17] are opposed to the designation "desensitization." They prefer the term hyposensitization, in recognition of the fact that this method has not solved the fundamental problem, namely—prevention of further antibody production upon which the continuance of the allergic state depends. Under certain conditions, however, hyposensitizing measures may lead to de-allergization (see below) as demonstrated by Dale[8] in animal experiments and confirmed in clinical practice. Sherman and Stull[23] achieved lasting insensitiveness in hay fever patients by means of very long courses of hyposensitization measures, creating a permanently raised threshold of tolerance to the antigen. But, in principle, the clinical results achieved with hyposensitization therapy still depend on regular administration of the antigen.

Our own investigations have convinced us that in the course of hyposensitization treatment there are certain phases during which, temporarily at least, the antibodies are totally neutralized. This is shown by the lack of reaction of the isolated uterus and lungs. Such phases are observed when a large deposit of antigen is being gradually absorbed by the organ-

ism. Further investigative studies will be necessary to determine just which hyposensitization methods can lead to permanent de-allergization.

If the antigen is not known or is an endogenous allergen, metaspecific hyposensitization may be attempted. This is based on systematic administration of minute, slowly increasing doses of hetero-allergens such as tuberculin, peptone and similar substances, producing a marked increase in the specific antibodies in the blood. The supposed antigen is thus prevented from entering into a reaction with the cellular antibodies, which, in turn impedes the occurrence of allergic manifestations. The experimental basis of this concept has been discussed in detail elsewhere.[29]

### METHODS OF SPECIFIC HYPOSENSITIZATION (DESENSITIZATION)

Hyposensitization can, in principle, be carried out in different ways. It is preferable to employ the route that will bring the antigen into direct contact with the organ primarily affected—the shock organ. We must differentiate, therefore, between the cutaneous (intracutaneous, subcutaneous), intramuscular, epidermal, oral, rectal, nasal, and bronchial routes of administration, choosing the route according to the particular shock organ.

Methods of hyposensitization consist essentially in administering—by injection, by application, or by spray—first a dilution of the antigen just strong enough to elicit a minute reaction in the shock organ, and in then repeating the administration when these manifestations of the antigen-antibody reaction have disappeared (about three to seven days). In this way, gradually increasing doses of antigen produce a marked increase in the organism's antibody titer, particularly with respect to circulating antibodies.

Intracutaneous and subcutaneous methods of hyposensitization are the best known and most widely employed procedures, intended to increase the antibody content of the blood. Until quite recently they were, for example, the only known approach in the anti-allergic treatment of hay fever and asthma. There is no sharply defined distinction between these two methods. Some authors prefer the intracutaneous route, because there is some evidence that the injected substance is absorbed more readily (Feinberg and Bernstein[10]) and because use of this route elicits more rapid and greater production of skin antibodies. However, the majority prefer the subcutaneous technique. The advantages of the latter are that it is less painful and that it permits the injection of a larger volume of the antigen extract. Both allow of precise dosage, in contrast to the cutaneous method.

For many years the intramuscular route for administration of antigen was neglected, but more recently it has been satisfactorily employed. Strickler[24] and numerous others have administered rhus toxin in this manner. And certain pollen and plant oils that evoke excessive reactions subcutaneously are often well tolerated when administered intramuscularly. Whether or not hyposensitization can be achieved in this manner is still a subject of considerable controversy. It is generally conceded,

however, that the principle underlying this method is sound. Thus Coca has succeeded in hyposensitizing a patient with turpentine allergy (house painter) by injecting turpentine dissolved in sterile almond oil every seven days.

The method of repeated epidermal application of the allergen was introduced by J. Jadassohn[14] who discovered that it was possible to achieve first a local and finally a general epidermal hyposensitization by means of repeated epidermal applications in slowly increasing concentrations. Gougerot successfully employed the epidermal route to hyposensitize patients with dermatitis due to rosewood, paraphenylene-diamine, and bichloride of mercury. Stuempke reported similar achievements in relation to dermatitis due to formalin, scarlet red, and tincture of arnica, and Schmidt in relation to mercury and tar dermatitis. Urbach was able to cure a weeping dermatitis due to hypersensitiveness to proteins coming from horses by systematic application of horse serum, sweat, hairs and dander, and also succeeded in completely hyposensitizing a patient with hypersensitiveness to arsenic. This method seems to have some significance in the prophylaxis of dermatitis due to flowers, grasses, weeds and woods. Thus Urbach reported successful hyposensitization in a case of hypersensitiveness to sage; Kadisch in a case of dermatitis due to tulips; Blumenthal and Jaffe in a case of allergy to oil of lavender; Maisel and also Shelmire, in dermatitis due to rhus toxicodendron; Touraine and Gole, in dermatitis due to a number of woods.

While the discussion above refers to the method of repeated epidermal application of the allergen as a form of hyposensitization, we feel that it may more properly be classified as de-allergization. However, since the necessary immunologic studies have not been carried out to demonstrate whether the titer of the circulating antibodies is increased or that of the tissue antibodies decreased as a result of this procedure, judgment must be suspended for the time being.

Oral hyposensitization consists of administration of minute quantities of the allergen and given daily in doses that are slowly and gradually increased every second to fourth day: the course of treatment is continued until tolerance to a normal amount of food is acquired. The success of this method depends largely upon the coöperation of the person responsible for its conduct, and thus to a considerable extent on the clarity of the instructions given by the physician. A detailed list of the foods containing the allergen in question should be supplied. Complete elimination of the allergen is essential, from inception of the treatment until its completion. A fresh solution should be prepared daily. If a reaction occurs, one reverts to a weaker dilution and then proceeds from that point according to the original schedule. After successful hyposensitization, the patient should make it a point to eat some of the particular food every day for several months. This method was successfully employed by Keston, Waters, Hopkins[16] and more recently by Edwards.[9] The course of treatment lasts often many months, and is, therefore, somewhat tedious. Good

results are reported by the peroral administration of pollens or pollen digests in hay fever. For some years attempts have been made to effect peroral hyposensitization in poison ivy, weed, and grass dermatitides. On the basis of the observation that farmers and gardeners hypersensitive to rhus are protected when they chew rhus leaves in the spring, Schamberg and later, Strickler recommended administration of a fluid extract of Rhus toxicodendron in increasing drop dosage. Spain and Cooke suggested a modification of this treatment—enteric coated rhus tablets—to minimize the danger of irritation of the oral and gastric mucous membranes. Urbach has obtained satisfactory results with enteric coated rhus seed extract. Especially extensive and valuable work in this field has been done by Shelmire.[22] He employs ivy oleoresin (1 per cent in a vegetable cooking oil) placed in an ordinary gelatin capsule. In the same way Shelmire treated dermatitides in which the cause was established as hypersensitiveness to the pollens of ragweed, cocklebur, and marsh elder, as well as to gaillardia leaves, by oral administration of the specific oleoresins. Trunell[25] and Sheldon and Blumenthal[21] confirmed the good results with this method. Finally, house dust allergy can be controlled by the peroral route (Barksdale,[1] Blackmar,[4] Urbach[29]).

## EXPERIMENTAL BASIS OF DE-ALLERGIZATION

The term de-allergization designates all the therapeutic measures by which antibodies actively produced by the organism are counteracted through the appropriate administration of antigen; the antibodies are thus neutralized or otherwise rendered incapable of reacting. This results first in the consumption of the tissue antibodies and later in the arrest of production of specific antibodies. In this manner, the entire organism (or the principal shock tissues) is rendered insensitive, permanently or for a certain length of time. Accordingly, we may differentiate between a total and a partial, and between a permanent and a temporary de-allergization. The three following combinations may result, and can be demonstrated by animal experiments: (1) the partial-temporary, (2) the total-temporary, (3) the total-permanent state of de-allergization.

In animal experiments, specific de-allergization can be achieved (1) by massive doses of specific antigen, causing severe macroshocks, (2) by injections of specific antigen, causing slight macroshocks, with a symptom-free state on subsequent massive doses of antigen, and (3) by means of specific skeptophylactic methods, acting through microshocks, (a) intravenously or (b) orally (Table I). It must be especially emphasized that de-allergization methods, at least at present, can be applied only when nonliving antigenic material is concerned.

## DE-ALLERGIZATION BY MASSIVE DOSES OF SPECIFIC ANTIGENS CAUSING SEVERE MACROSHOCKS

De-allergization by means of overloading with antigens succeeds only when the proper dose of antigen has been chosen for reinjection—that is, when the dose brings on a severe anaphylactic shock that, however, does

not cause immediate death, but is either followed by death after one to two hours, or by ultimate survival of the animal after the most severe and long-lasting manifestations. As demonstrated by the lung perfusion experiment (Urbach)[28], as well as by the Schultz-Dale test, the organs of an animal thus exposed to long-lasting shock become de-allergized for the duration of its life—in other words, no antigen-antibody reaction occuurs. If, on the other hand, the reinjection brings on acute, lethal anaphylactic shock, the lungs and uterus of the animal are found to be highly sensitive.

The results of these two experiments conform perfectly with the theoretic expectations. For, in the case of lethal shock, there is insufficient time for the tissue antibodies to be neutralized by the administered antigen, while, in case of survival, the slow neutralization brings about total and permanent specific insensitiveness of the lungs and uterus.

### DE-ALLERGIZATION BY INJECTIONS OF SPECIFIC ANTIGEN LEADING TO SLIGHT MACROSHOCKS: SYMPTOM-FREE STATE ON SUBSEQUENT MASSIVE DOSES OF ANTIGEN

In the course of anti-allergic treatment, it is possible, either accidentally or intentionally, that the first or one of the later injections may cause clinical anaphylactic manifestations, even though slight. In such a case, the animal will be completely refractory to a reinjection with the multiple of the lethal dose—provided the reinjection is not given until after four hours have elapsed. The basic mechanism here is different, however, from that which results in protection from skeptophylactic injections. For reinjection with a lethal dose (after four hours), in animals that have survived such slight macroshocks, shows these animals to be totally de-allergized—i.e., no antibodies can be found in the lungs or uterus, nor can the hypersensitiveness be transferred. On the other hand in guinea pigs treated skeptophylactically by intravenous injections the uterus contains abundant antibodies (positive Schultz-Dale test), and the hypersensitiveness can be transferred passively by way of the blood serum. Moreover, prior to this reinjection, there is only a partial de-allergization of the lungs, as shown by negative results in the lung perfusion test.

The mechanism of de-allergization by means of antigen injections eliciting distinct although slight anaphylactic manifestations, in contrast to the classic skeptophylactic methods, may be explained by the following hypothesis:

Recovery from even a mild macroshock brings about a temporary satiation of the antibodies of the primary shock tissues (as demonstrated by the negative outcome of the lung perfusion experiment). In addition, as will be described below, this prepares for an alteration in all antibody-containing tissues, so that the further administration of antigen results, at least for a certain time, in a state of total de-allergization. This may be demonstrated by the absence of antibodies in the blood serum, by the absence of the specific uterine reaction in the Schultz-Dale experiment, and by the negative outcome of the lung perfusion experiment.

*(To be continued in next issue.)*

# SOME OF THE FACTORS TO BE CONSIDERED IN THE ETIOLOGY OF BRONCHIAL ASTHMA

## A TENTATIVE CLASSIFICATION

ETHAN ALLAN BROWN, M.D.†, and P. LIONEL GOITEIN, M.D.‡

BOSTON, MASSACHUSETTS

THERE are few conditions in medicine as complex as those due to allergy. If we review in their simplest forms the more fundamental facts regarding one particular syndrome, such as bronchial asthma, it is obvious that the asthmatic patient reacts with a wheeze to substances and circumstances which have no demonstrable effect upon so-called normal individuals.

In allergy, generally speaking, almost any part of the patient's body may be affected, the symptoms depending upon the degree of spasm or the edema of the organ involved. In bronchial asthma, the shock organ (in this case, the lungs) may become a battleground for a number of conflicting stimuli, among others, those due to allergy, infection, structural changes, and physical and psychic influences as well as those referred to the pulmonary system from other parts of the body. To all of these, the patient responds with a single sign, a wheeze.

When the causes for a condition are many but the symptoms few, the therapeutic tests are necessarily inconclusive. Any treatment which lightens the patient's burden has a fair chance of relieving him of much of his distress. A patient who is clinically sensitive to feathers may be helped by psychotherapy, while others in whom the psychic element is important are nevertheless improved by a hygienic régime or by symptomatic medication. In both of these types of treatment there are, of course, psychic factors only too often minimized, if not ignored.

Knowledge of the many contributing factors in bronchial asthma changes our conception of the condition, making our definitions more and more broad. Not only are we extending the number of phenomena termed allergic, but we are forced to an ever-increasing degree, to talk of "allergy as seen in pollinosis, as typified by tuberculosis, as exemplified in bronchial asthma, as presented in contact dermatitis, and as manifested in certain behavior patterns." On the other hand, buried beneath these seemingly complex phenomena there may be some unifying principles which will "explain" everything. At present, no such explanation is in sight, but on the contrary, the multitudinous attempts at explanation are scattered in publications so widely divergent in subject matter that few of us realize how widely spread they really are. Other reviews, of course,

The incidental expenses for this work were defrayed in part by a grant from the Asthma Research Foundation, Inc., Boston, Massachusetts.

†Physician-in-Chief, Allergy Department, New England Medical Center, Boston.
‡Assistant Physician, Nerve Department, New England Medical Center, Boston.

have been written, but these naturally enough have portrayed the special interest of the reviewer. Among others, to take three reviews of purely psychologic medicine, Dunbar's survey emphasizes psychogenic factors, while Wittkower stresses environmental influences, and Alexander accents the analysis of personality.

At first glance the tables will seem incredibly confusing. Relatively unimportant or little known facts, by their very listing, are given an importance apparently equal to that of "accepted knowledge," a fault inherent in any attempt to make a small scale map in which a mountain peak and a village may both be represented by a dot. A future paper in the present series will furnish a large scale map for each of the groups of concepts given. The present paper should be viewed as an attempt to be comprehensive for general factors rather than all-inclusive for specific details. For example, inhalant allergy is mentioned briefly, but no list of all the known allergy-causing inhalants is given. In the same way, some 300 causal factors are listed in eight large groups, the headings for which are self-explanatory.

1.

ONTOGENIC

or

DEVELOPMENTAL LEVEL

1. Trauma (psychic), effect of whooping cough or bronchitis ..... Deutsch
2. Trauma (external), effect of familial births and deaths ..... Jones
3. Crises in family life (precipitates attack) ..... Strauss
   Stresses, threats ..... Weiss
   Infancy seductions ..... Bacon
   Quarrels, reproofs ..... Mohr
4. Biologic milestones
   Food-forcing ..... Oberndorf
   Puberty ..... Dunbar
   Menstruation ..... Hoseason
   Habits (pre-genital) characterologic predisposition ..... Shultz
   Pylorospasm ..... Todd
5. Oral frustration ..... Dunbar
   Suckling trauma ..... Ophuijsen
   Breast-Stifling ..... Harnik
   Incorporation phantasy ..... French
   Birth trauma ..... Rank
   "Cell-memory" ..... Jelliffe
   Regression (analytic) ..... Michaels
6. Intra-uterine constraint (suffocation-cry) ..... Snyder
7. Fetal breathing-pattern ..... Windle
   Placental permeation ..... Ratner
8. "Stuffy atmosphere inside womb" and "dying gasp" paradox ..... Barcroft
   Fear of water and drowning ..... Alexander

2.

PHYLOGENIC

or

AFFECTIVE LEVEL

1. ENVIRONMENTAL (Mental)
   Parental solicitude
   Maternal rejection ..... Mohr
   Race (social level)
   scholastic stress ..... Strauss
   Suggestion ..... MacKenzie
   Overtenderness ..... Oberndorf
   Solitary-shyness ..... Rogerson
   Sensitivity (irritability) ..... Brauns
   Emotional tenderness ..... Ziegler
2. PSYCHOGENIC PRECIPITANTS
   Emotional conflict ..... French
   "Typical character traits" (before, during, and after onset) ..... Wittkower
3. PURPOSIVE ATTACKS
   Instinctual motivation for
   domination ..... Bingermann
   Aggression ..... Clarkson
   Hostility ..... Rogerson
   Sympathy ..... Freudenberg
   Self-punishment ..... Jolowicz
   Pampering ..... Strauss
   Withdrawal ..... Bacon
4. PAROXYSMS serve as:
   Orgasmic ..... Many authors
   Purposive ..... Gillespie
   Protest ..... Rogerson
   Guilt-release ..... Hansen
   Death-wish ..... Wulf
   "Separation anxiety" ..... Kronfeld
   "Temptation anxiety" ..... Kronfeld
   "Conversion neurosis" ..... Dunbar
   "Narcissistic neurosis" ..... Fenichel
   "Organ compliance" ..... Freud

Suggestion .....Rober
"Psychic equivalent of colds" .....Marcinowski
"Coitus equivalent".....French
"Formes frustes".....Menninger
"Dispositional conditioning" .....Deutsch
Secondary allergy.....Sampliner
Fixation aggression (oral phase) .....Fenichel
Personality changes.....Stokes

---

## 3.

BIOGENIC

or

SYMBOLIC LEVEL

1. BIOLOGICAL CAUSES
   Animal hair .....Lautreamont
   Mice .....Lintz
   "Seeds" .....Gutheil
   Moulds .....Feinberg
   "Milk" .....Coke
   "Damp" .....Hansen
   Heights .....Laudenheimer
   Barometric changes.....Peterson
   Glue .....Andrews
   Silk .....Clarke
   Paper .....Bennett
   Dust .....Cooke
   Moths .....Parlato
   Odors .....Urbach
   (Only representative allergens are listed.)
2. "Repetition compulsion".....Galup
3. "Sexual neurosis".....Sadger
4. "Embarrassment" and anxiety
   "Vital capacity" lower....Many authors
   "Foreign body" on chest....Korperreiz
   "Angst" and anoxemia.....Binger
5. Emotional trauma.....Naber
6. Psychic anaphylaxis.....Velikovsky
7. OCCUPATION NEUROSIS.....Moos
   Digitalis (nurses) .....Brodsky
   Dust (housewives) .....Cohen
   Flour (millers) .....Diaz
   Paraldehyde (druggist).....Peshkin
   Garlic (grocer) .....Henson
   (Many more inhalant and food allergens may be acting in this manner than is commonly suspected.)

---

## 4.

HUMOROGENIC

or

CHEMICAL EMPHASIS

1. METABOLIC CHANGES
   "Humors" irritate the lung.....Galen
   Blood K-P (increase).....Hansen
   Tissue Ca. and Mg. (decrease) .....Pottenger
   Biochemical changes (cholesterol) .....Barber
   Tissue alkalosis .....Kern
2. "Eosinophilic diathesis".....Staubli
   Hemaglobinuria .....Jones
3. Protein hypersensitivity.....Rudolph
4. Histamine cellular antigens, reagins .....Baldwin
   Atopens .....Coca
   Bacterial proteins .....Bethea
   Mucinogen coagulant oxydase .....Harkavy
   "P" substance.....Orie!
5. ENDOCRINES .....Selfridge
   Pituitary (hypo).....Goldzieher
   Ovary .....Cahane
   Thyroid (excess) .....Galup
   Parathyroid .....Jelliffe
   Suprarenal cortex.....Rudolph
   Pregnancy (lutein) .....Green
   Menopause (ovary).....Ross
   (A supposedly causal relationship to almost any change in every endocrine organ in the body has at some time or other been described, in the majority of cases, on slight evidence.)

---

## 5.

CYTOGENIC

or

TISSUE LEVEL

1. MEMBRANES
   Permeability increased.....Tuft
   Membrane swelling.....Costa
   "Secretary neurosis" .....Weber
   Visceral spasm .....Hoseason
2. MUSCLE SPASM
   Bronchiole .....Decourt
   Fluid disturbance (local retention) .....Abbott
   Pulmonary circulation.....Galindez
3. DIAPHRAGM
   Spasm .....Wintrich
   Broncho-stenosis .....Prickman
4. CONSTITUTIONAL FACTORS
   "Exudative diathesis".....Eppinger
   Special somato-type .....Young
   Asthenic typus .....Kretschmer
   Lepto-somatic .....Goldzieher
   Biopsychic (types).....Draper
   "Disposition and threshold" .....Fraenkel
   Bowel absorption of toxic allergens .....Eustis
   Enteritis .....Hansen
5. COINCIDENTAL CONDITIONS
   "Hyperesthetic rhinitis".....Hazelton
   Oedemas .....Diehl
   Urticaria .....Rogerson
   Tubercle (rare).....Bray
   Hepatic deficiency .....Farago
   (This list excludes, of course, other conditions known with certainty to be allergic in origin.)

## 6.

SOMATOGENIC

or

SYMPTOM LEVEL

"Violent motion of body and mind" ..... Willisius

1. EXTERNAL CAUSATION
   - seasons ..... Cobe
   - Latitudes ..... Vanleeuwen
   - Proteins (ingested) ..... Duke
   - Dust (inhaled) ..... Cooke
   - Temperature ..... Horton
   - Stuffy atmosphere ..... Tidy
   - Occupation ..... Forker
   - Exertion ..... Livingstone
2. INTERNAL CAUSATION
   - Allergy and anaphylaxis ..... Meltzer
   - Innate factors ..... Strumpell
   - Heredity ..... Bray
   - Infection ..... Knott
   - Bronchitis ..... Chobot
   - Desensitization ..... Brown
   - Adenoids ..... Steinberg
   - Sinusitis ..... Hansel
   - Toxicity ..... McGregor
3. IDIOPATHY (General)
   - Somatic diathesis ..... Strumpell
   - Anatomic disturbance ..... Cabello
4. ORGAN
   - Pulmonary predisposition ..... Fraenkel
   - Whooping cough ..... Marx
   - Bronchitis (bacterial) ..... Steinberg
   - Bronchitis (allergic) ..... Walker
   - Nose (obstruction) ..... Maxwell
   - Rhinorrhoea ..... Hoseason
   - Polypi ..... Brugelmann
   - Emphysema (bronchiectasis) .... Chobot
5. GENERAL FACTORS
   - Vasomotor instability ..... Moll
   - Spasticity ..... Clarkson
   - Heredity (germ-plasm) ..... Balyeat
   - Blood pressure ..... Witts
   - Reflex (appendix) ..... Tuft
   - Colic (biliary) ..... Garnier

(Every reader will, without doubt, recall additional references which should have been included in this and the remaining columns.)

---

## 7.

NEUROGENIC

or

NERVOUS CONCEPTION OF ASTHMA

1. CENTRAL DISTURBANCES
   - "Nervous spasmodic asthma" ..... Van Helmont
   - "Nervous pseudoasthma" ..... Dejerine
   - Autonomic hyperirritability ..... Salter
   - Vegetative dyscrasia ..... Brauns
   - Visceral excitability ..... Pollnow
   - Vagal nucleus disturbance ..... Hurst
   - Vagotonia ..... Wolfe
   - Visceral spasm ..... Decourt
   - "Sympathicotonia" ..... Jacquelin
   - Angio-neurosis ..... Jones
   - Respiratory center disturbance ..... Laudenheimer
   - Hyper-ventilation ..... Kerr
   - "Reflex neurosis" ..... Curshmann
   - "Bulbar neurosis" ..... Eichorst
   - Non-passive respiration ..... Brown
   - Extrapyramidal involvement ..... Joslin
   - "Spasm" center disturbance ..... Marx
2. LOCAL ABNORMALITIES
   - "Conditioned reflex" ..... Metalnikov
   - "Ganglionic plexus" ..... Binger
   - "Detonator action" ..... Freeman
   - "Trigger reflex" ..... Hazelton
   - "Conditioning" ..... Bernard
   - Expectation ..... Hurst
   - "Nervous asthma" ..... Dekker
3. COINCIDENTAL CONDITIONS
   - Epilepsy ..... Costelio
   - Stuttering ..... Kennedy
   - Migraine ..... Rowe
   - Psycho-neuroses ..... Costa
   - Imitativeness ..... Gillespie
   - Hysterias ..... Yaskin
   - Psychoses ..... DeRiver
   - "Organ inferiority" ..... Adler
   - Sinistrability ..... Alexander

(Coincidental conditions have frequently been described as being causally related. Time has shown many of these to have been linked chronologically and by no other relationship.)

---

## 8.

PSYCHOGENIC

or

PSYCHOSOMATIC LEVEL

1. PRE-DISPOSITION ..... Gillespie
   - By mental heredity ..... Culpin
   - By hypersensitivity (psychic) ..... Eyermann
2. PSYCHOSOMATIC FEATURES
   - Consequent upon physical factors ..... Cobb
   - Breathing type (special) .... Livingstone
   - On "mental heredity" ..... Rogerson
   - Familial relationship as
     - The "Only" child ..... Adam
     - The eldest child ..... Strauss
3. CORRELATION (Psychic)
   - Cyclothymia ..... Reichman
   - Obsessionalism ..... Laennec
   - Hysteria ..... Freud
   - Paranoia ..... Deutsch
   - Precox (rarity) ..... Nickum
   - "Hysteric psychosis" ..... Edel
   - Over-anxiety ..... Pearson

(The recent surge in psychosomatic medicine is rapidly extending the list of psychogenic causes.)

The vast amount of material available had to be compressed, if it was to be at all manageable. Key words or phrases had to be invented to designate entire papers and, in some cases, an entire series of papers by a single author who referred to a single aspect of allergy. As in all classifications, the key phrases are not necessarily placed in a list of the original authors' choosing but rather where the present writers thought they might best fit. Many of the listings undoubtedly belong in several columns.

It may surprise some readers to find inhalants listed under "symbolic" concepts. This is not purely the authors' personal choice, since work published by others has shown the patient "psychologically sensitive" to the concept behind the causative substance. Our own work, now in process of publication, also stresses such psychologic sensitivity. The authors of the original papers listed do not, therefore, necessarily exemplify such symbolism. The listing itself, therefore, must be considered more important than its actual location in the general classification. Changing conceptions of allergy will, of course, necessitate changes in emphasis.

For any given reference the author chosen is not necessarily the original or sole worker who first emphasized the aspect of allergy we have linked with his name, nor need he be accepted as the best exemplar of the causal nexus chosen. In no case does a listing imply that the author stresses one single factor or excludes all other possible factors. The bibliography is full, and the landmarks given will, of themselves, furnish others which will take the interested reader into new and fascinating areas of intellectual exploration. This summary in tabular form will, in any case, serve to remind us of the complexity of the problems involved in the diagnosis and treatment of bronchial asthma.

## BIBLIOGRAPHIES

Bibliographies of the authorities referred to have been made repeatedly and are chiefly to be found with full titles in the following sources:

Dunbar, H. F.: Emotions and Bodily Changes. A Survey of Literature of Psychosomatic Relationships. New York: Columbia Univ. Press, 1938.
Feinberg, S. M.: Asthma and hay fever—Annual Review of Literature for 1937-1940 (with Bernstein, M.D.), J. Allergy, Vols. **8, 9, 10** and **11**.
French, T. M.: Psychogenic factors in bronchial asthma, Psychosomatic Medicine, Monograph IV, 1, 1941.
Tuft, L.: Clinical Allergy. Philadelphia: W. B. Saunders Co., 1937.
Wittkower, E.: Studies on the influence of emotions on the functions of organs. J. Ment. Sci., **81**:523-682, 1935.

## SELECTED REFERENCES†

Alexander, F.: Psychosomatic Medicine, Monograph IV, Part 1, 1941.

Barcroft, J.: Physiol., **93**:21-22, 1938.
Bennett, T.: New England J. Med., **213**:121, (July) 1935.
Binger, C.: Ann. Int. Med., **11**:195, (July) 1937.
Brauns, A.: Med. Welt., **7**:559, 1933.
Bray, G.: Recent Advances in Allergy, 3rd ed. Blakiston, 1937.
Brown, Orville: Asthma. St. Louis: C. V. Mosby Co., 1917.

Cahane, M.: Rev. franc, d'endocrinol, **17**:301, (October) 1939.
Chicago News: J.A.M.A., p. 115 (quoted), (November) 1940.
Chobot, R.: Am. J. Dis. Child, **52**:882, (January) 1936.

†The bibliographies given by the authors of the references cited will repay careful study.

Clarke, J.: J.A.M.A., **80**:11, 1923.
Clarkson, A. K.: Brit. M. J, **2**:845, 1937.
Cobb, S.: Psychosomatic Med., 1:203, (April) 1939.
Cobe, H.: J. Allergy, 1:442, 1930.
Coca, A.: Arch. Path. & Int. Med., 1:96, 1926.
Coke, F.: Brit. M. J., 1:955, 1927
Cooke, R.: J. Immunol., 7:147, 1927.
Costello, K.: Lancet, p. 1660, (March) 1938.

Dekker, H.: München med. Wchnschr., **81**:323, 1934.
DeRiver, J.: New York State J. Med., **117**:730, 1923.
Deutsch, F.: J. Res. N. Ment. Dis., p. 19, (September) 1939.
Diehl, H.: München med. Wchnschr., **78**:1008, 1931
Duke, W.: Allergy, Asthma and Hay Fever. St. Louis: C. V. Mosby Co., 1925.
Dunbar, F.: Psychoanalyt. Quart., p. 725, (January) 1938.

Eustis, A.: New Orleans M. & S. J., **92**:349, 1940.
Eyermann, C.: J. Allergy, 9:565-571, (September) 1938.

Feinberg, S.: J. Allergy, **8, 9, 19,** and **11**: (March) 1937 to 1940.
Fenichel, O.: Hysterien und Zwangsneurosen. Wien, 1931.
Fraenkel, E.: Brit. M. J., 1:438-441, (February) 1937.
Freeman, J.: Proc. Roy. Soc. Med., **28**:247, 1935.
French, T.: Am. J. Psychiat., **96**:87, (July) 1939.

Galup, J.: Progrès méd., p. 662, (April) 1931.
Galup, P.: Gaz. méd. de France, **44**:403, 1937.
Gillespie, R.: Brit. M. J., 1:1285, 1935.
Goldzieher, M.: Practical Endocrinology. New York: Century Press, 1935.
Green, P.: J.A.M.A., **102**:360, 1934.

Hanse, A.: München med. Wchnschr., **82**:1985-2030, (December) 1935.
Hansen, K.: Proc. Roy. Soc. Med., **22**:789, 1929.
Horton, B.: Quoted Tuft, 1937.
Hoseason, A.: Brit. M. J., 2:703-704, (October) 1938.

Insley, S.: J. Michigan M. Soc., **33**:384, (July) 1934.

Jacquelin, J.: Monde méd., Paris, (June 1) 1938.
Jelliffe, S.: Am. J. Psychiat., **92**:5, 1051, 1935.
Jones, H.: Glasgow, M. J., **123**:254, 1935.

Kennedy, A.: Brit. M. J., 2:1306, (December) 1938.
Kretschmer, E.: Brit. M. J., 2:403, 1937.

Laudenheimer: Quoted Dunbar, 1938.
Lautréamont: Fleurs de Maldoror, Paris: 1760.
Lintz, W.: New York State J. Med., **117**:729, (June) 1923.
Livingstone, J.: Proc. Roy. Soc. Med., **28**:249, (September) 1935.

Marcinowski, J.: Deutsch. med. Wchnschr., **49**:477, 1923.
Metalnikov, S.: Presse, méd., **42**:1893, (November) 1934.
Michaels, J.: Personal communication, 1940.
Moll, H.: Brit. M. J., 2:299, 1934.
Moos, E.: München med. Wchnschr., **70**:805, 1923.

Nickum, O.: Nebraska S. M. J., **19**:224, (June) 1934.

Oberndorf, C.: N. Y. State J. Med., **35**:41, (January) 1935.

Peterson: The Patient and the Weather. Ann Arbor, Mich.: Edwards Brothers, Inc., 1934-1937.
Pollnow, H.: Zetschr. f. klin Med., **110**:701, 1929
Pottenger, F.: Am. J. Med. Sc., **95**:417, 1918.

Ramirez, M.: Arch. Int. Med., **142**:368, 1928.
Ratner, B.: J. Pediat., **16**:653, 1940.
Reichmann, F.: Med. Klin., **18**:1090-1092, 1922.
Rogerson, C.: Quart. J. Med., 6:367, (October) 1937.
Ross, J.: Brit. N. J., 1:12, 1922.

Sadger, J.: Zentralbl. f. Psychoanal., 1:200-213, 1911.
Sampliner, R.: Psychiatric Quart., **13**:3, 521, 1939.
Saul, L.: Psychosomatic Med., **31**:66, 1941.
Selfridge, G.: Calif. State J. Med., **17**:105, 1919.
Snyder, F.: Am. J. Physiol., **119**:153-157, (May) 1937
Stevens, F.: J. Pediat., **14**:307, (March) 1939.
Strauss, E.: Guy's Hosp. Rep., **5**:289 and 309, 1935.
Strümpell, A.: Quoted Dunbar, 1938.

Tuft, L.: Clinical Allergy. Philadelphia: W. B. Saunders Co., 1937.

Weiss, E.: Internat. Ztschr. (arztl) Psychoanal., **8**:440, 1922.
Wintrich: Quoted Dunbar, 1938.
Wittkower, E.: J. Ment. Sci., **81**:533-682, 1935.
Witts, L.: Lancet, 1:375, 1934.
Wolfe, J. A.: Am. Med., **40**:432 and **41**:312, (October) 1934.

Yearsley, M.: Brit. J. Child. Dis., **36**:106, (April) 1936.
Young, M.: J. Hyg., p. 933, 1933.

Ziegler, L H.: Am. J. M. Sc., **172**:8600, 1926.

# VERNAL CONJUNCTIVITIS (SPRING OR VERNAL CATARRH)

SAMUEL MARTON, M.D.
NEW YORK, N. Y.

VERNAL conjunctivitis as a clinical entity has been recognized for many years. It was first described by Arlt (1846) as conjunctivitis lymphatica. Saemisch (1875) recognized its periodicity and named the condition spring catarrh. The term, still retained today, is not a satisfactory one because the symptoms are not confined solely to the spring of the year nor is the exudate catarrhal in nature. The etiology and method of treatment are still subjects of much controversy.

Clinically it is characterized by a history of seasonal recurrence with symptoms confined to either the tarsal or limbal portions of the conjunctiva. The onset may be bilateral or unilateral, most frequently the former. In the acute tarsal stage there is an interstitial inflammation of the conjunctiva, accompanied by redness of the eyes, itching, lacrimation and a mucoid discharge. In the chronic stage large papules (globular, discrete or clumped) form on the tarsal conjunctiva and the discharge changes to a "chewing gum" or lardaceous type, dirty white to cream in color. The discharge contains mucus, epithelial cells, mononuclear leukocytes, polymorphonuclear leukocytes and eosinophiles. It is at this stage that vernal conjunctivitis is confused with trachoma. If the condition is allowed to progress unchecked the papules become flat topped or cobblestone in appearance. This is due to connective tissue proliferation and infiltration of the follicles.

As to the etiology there have been many and diverse theories. In the early 1900's the cause was thought to be direct action of light, ultra violet rays, heat and a disturbance of the endocrine glands. However, in more recent times the hypothesis has been veering towards allergy as the basic causative factor of vernal conjunctivitis. Fort (1923) reported nineteen cases, all of which showed pollen sensitization. Lemoine (1925) reported a series of cases in which only one proved to have a positive pollen reaction. Townsend (1923) reported that most of his cases were pollen sensitive. Thommen (1931) on the other hand, reported the opposite. Lehrfeld, in 1931 and again in 1932, stated that 10 per cent of his cases of vernal conjunctivitis were definitely allergic. In Berens' textbook "The Eye and Its Diseases" (1936), S. Hanford McKee makes the following statement: "It is related to summer weather, but whether mostly to heat or light is not known." Balyeat and Bowen (1935), in their paper discussing all types of allergic conjunctivitis, reported a case sensitive to pollen. Duke-Elder (1938) believes the most plausible hypothesis is that vernal conjunctivitis is a conjunctival manifestation of an allergy, the irritating agent being dust aggravated by heat occurring preferentially in vagotonic individuals.

Since the vast majority of patients with vernal conjunctivitis are seen and treated primarily by the ophthalmologist it is interesting to note their suggested modes of treatment. Berens and McKee (1936) make the following statement: "In general the disease is incurable and palliation of the acute symptoms represents about all that can be done. By the use of radium, however, the prognosis has been greatly improved and the chance of limiting the course of the disease much enhanced. Radium has been used by Davidson, Lawson, Janeway and others with satisfactory results." For the milder cases they advise routine palliative solutions. Weiner (1935) suggests the use of optochine, ice water applications, or radium. Duke-Elder (1938) stated the following: "It may be said at once that there is no specific treatment for vernal conjunctivitis; the most that can be done is to use palliatives until the disease dies down itself. The most efficient treatment of all is to change from a hot to a cold climate and to migrate seasonally." Other methods that he advises besides the usual routine local palliatives are radium treatment and surgical removal of the large vegetative growths. These regimens are apparently the modus operandi of a great majority of the ophthalmologists. However, Lehrfeld (1932) concluded that vernal conjunctivitis is an ocular manifestation of an allergy and that the treatment of this disease belongs to the allergist.

The following case histories are presented in support of pollen as the prime etiologic factor of vernal conjunctivitis.

*Case 1.*—The patient, a boy seven years of age, was first seen by me in August, 1936. The history was as follows: At the age of two years in June or the latter part of May, 1931, his eyes began to water and itch. As the months wore on, photophobia became so aggravated that he could not stand light of any sort. Even the glare of snow was too much for him. Lacrimation was so severe that the skin of his cheeks became excoriated. Several ophthalmologists were seen without relief. In 1932, symptoms continued unabated with exacerbation in the spring and fall. The year 1933 was a repetition of 1932. The following year the child was taken to an eye clinic where a tarsal resection was done on both eyelids because he had "lumps" on them; however, the symptoms continued unabated. Repeated ulcers occurred in the left cornea. By this time the child had to be led by his hand, for he was unable to open his eyes in the presence of any light.

Examination of the eyes showed thickening of the upper lids, the tarsal conjunctiva were markedly injected and studded with small follicles. Both corneas were slightly dull with punctate keratitis. The discharge was of a thick mucoid, stringy "chewing gum" type, with moderate number of eosinophiles, epithelial cells, mononuclear leukocytes and some polymorphonuclear leukocytes. A complete blood count was found to be normal. Wassermann and Kahn tests were negative. Family history was negative for allergy. Pollen tests with the scratch and intradermal techniques were negative. Because of the history, treatment was immediately begun with injections of 1-5000 red oak, grasses (timothy, red top, orchard, June) and ragweed. No local palliative treatment was instituted because the mother stated that anything touching the eyes immediately aggravated the symptoms. Dosages were rapidly stepped up, so that by the end of the fifth week he was well in the 1-50 dilutions. By this time, with the aid of colored glasses, he was able to go about alone and the ocular discharge became much thinner. The boy was as yet unable to enter school because any attempt at learning was attended by severe lacrimation. At the

end of three months of treatment photophobia was practically absent and only occasionally did tearing occur. The redness of the tarsal conjunctiva was markedly decreased but the small follicles were still of the same size. The injections were continued perennially. He did very well the next year (1937) except for a slight occasional exacerbation during the ensuing pollen seasons. Home teaching was instituted because any prolonged attempt at studying was still accompanied by lacrimation. Treatment was continued with good results except for occasional slight eye irritation in June and September, 1938. The tarsal conjunctiva was now practically free of follicles and the color was practically normal. The following year showed continued improvement over 1938. There were no eye symptoms in 1940, 1941, and 1942. The patient was last examined on May 13, 1942 and both eyes were perfectly normal. All signs of a local pathologic condition had cleared up.

*Case 2.*—This patient, a man aged twenty-nine, married, was unable to earn a livelihood because of his severe visual disability. He has had eczema of the face, cubital and popliteal areas, since early childhood. A niece has hay fever and asthma. He was well, except for eczema, until June, 1938, when his eyes began to water and itch with an accompanying mucoid discharge. After some relief between July 15 and August 15 the symptoms flared up again. This lasted until cold weather set in. The following year the same cycle returned and from then on the symptoms became perennial. He was told by an ophthalmologist that he had trachoma and that nothing could be done about it. I first saw the patient on July 16, 1941. Because of marked photophobia he was literally blind and had to be led by his arm. His eyes presented the following signs: Conjunctiva thickened, deep pink color, several shreds of psuedo-membrane. A few flattened whitish papillæ were on the right lower lid and one on the left lower lid. Each upper lid was studded with large flattened papillæ, many of which were milky white with the intervening tissue of the same color. The left upper lid had a lesser number of papillæ. There was a little reticular injection of the bulbar portion. Each eye showed a punctate keratitis. There was also a large ulcerated area in the right cornea. The discharge was lardaceous in type and contained numerous eosinophiles. Wassermann and Kahn tests were negative and a complete blood count was done and found to be normal. He was tested and found faintly positive intradermally to short and giant ragweed and June grass. Injections were begun July 18, 1942, with extracts of ragweed and grasses (timothy, redtop, orchard, June) and rapidly worked up so that in a few months he was able to take a dose of 1-33 dilution (2 c.c.). At the same time local treatment of the ulcer by the referring ophthalmologist with topical application of 88 per cent phenol and sulfathiazole orally healed the ulcer by September. His eye symptoms were 75 per cent improved by October. However, the cobblestone appearance of the tarsal conjunctiva were still very much in evidence and on October 6, 1942, the ophthalmologist removed some granulation tissue from the right tarsal conjunctiva. The injections with grasses and ragweed were continued perennially and he was able to go through 1942 without any further trouble except for occasional slight itching and watering of the eyes. At present, he is still under perennial treatment and is feeling quite well. The cobblestone appearance of the tarsal conjunctiva is still present, but the condition shows great improvement.

*Case 3.*—A woman, aged thirty-eight, married, was referred July 17, 1942. Her sister's child had hay fever. She was well until June, 1941, when her eyes began to tear and itch. This lasted all summer and then greatly lessened during the winter months. Since May 30, 1942, her condition became markedly worse, accompanied now by stringy, mucoid discharge and severe photophobia. She went to a few ophthalmologists who told her she had trachoma. Local treatment was administered by them without relief.

Upon examination the lids were found to be thickened with horizontal wrinkling.

The conjunctiva showed moderate injection of the tarsal portion with numerous small follicles, the latter being larger in size in the left eye. In the right upper lid there was also a large flat papule. Both corneas were slightly dull with punctate keratitis. A few eosinophiles were found in the eye smear. Pollen skin tests were all found negative. Because of the history treatment was immediately begun with extracts of grasses (timothy, redtop, orchard and June) and ragweed. The injections were given daily for two weeks and then three times a week so that by August 10 a strong concentration of both extracts was being given (1 c.c. of 1-50 dilution). Within a few days after initiation of treatment the symptoms were ameliorating. By the end of September the left eye was entirely cleared of all discharge, although there was still a slight mucoid discharge from the right eye. From October 30 to the present time the patient has been free of all symptoms. The follicles are undergoing involution. She is still on perennial treatment.

*Case 4.*—A woman aged thirty-nine, married, was referred on March 12, 1940. There was no allergic history in the family. The patient complained of slight itching of the eyes for a number of years, beginning at the end of May and lasting through June, July, August and September. This cycle recurred each year. For the past few years it had been getting progressively worse, more severe in June and July, and was accompanied by a stringy discharge. There was mild photophobia. Physical examination revealed a moderately injected tarsal conjunctivitis with a few scattered follicles. A few eosinophiles were present in the eye smear. Pollen tests by the scratch method were positive to timothy, redtop, orchard, June, hickory; intradermal was faintly positive to ragweed. Injections were started with hickory, grasses and ragweed on March 4, 1940, and rapidly worked up so that by May 13 she was receiving 0.5 c.c. of 1-50 hickory, by June 1 1.2 c.c. of 1-50 grasses and by August 15 1 c.c. of 1-50 ragweed. She went through the pollen season without any further trouble except for an occasional eye itch and, very rarely, some mucoid discharge. The patient was kept on perennial treatment. The pollen seasons of 1941 and 1942 were symptom-free but for an occasional itching of the eyes. The discharge had entirely disappeared and at present there are no longer any follicles.

## COMMENT

I have carefully avoided reporting any cases that might have any resemblance to hay fever itself; i.e., there were many other cases with eye symptoms that had associated slight sneezing. These were not considered a true picture of the distinct entity, vernal conjunctivitis.

Though Lehrfeld, Balyeat, Bowen and others have brought sharp attention to the differential diagnosis between trachoma and vernal conjunctivitis, the mistaken diagnosis of the former for the latter is still being made. The cardinal point in the differentiation is the history. If the onset of the disturbance is in a pollinating season with aggravation of symptoms in succeeding seasons and despite negative tests, the diagnosis of vernal conjunctivitis must be made.

From the presentation of these cases it can be readily seen that specific treatment with extracts of the offending pollens can bring quick and ultimate permanent relief to these physically and economically distressed patients. If the pathologic change in the tarsal conjunctiva is very great or if corneal ulcer is present, the aid of the ophthalmologist with local surgical or topical treatment is necessary.

*(Continued on Page 62)*

# EMPIRICAL FORMULA, STRUCTURAL FORMULA, AND MOLECULAR WEIGHT OF THE MAJOR ANTIGEN IN CRUDE RAGWEED POLLEN EXTRACT

GEORGE E. ROCKWELL, M.D.
CINCINNATI, OHIO

SINCE Blackley[7] published his book on hay fever in 1873, there has been an ever-increasing interest in the chemical nature of the active antigen of pollen. Kammann[25,26] in 1904-06 investigated the chemistry of rye pollen and made quantitative analyses for water, ash, and organic material and the distribution of the latter as protein, nonprotein nitrogenous material, and carbohydrate. This work led him to believe that the activity was in the protein fraction. His active material was precipitated from solution only by full saturation with ammonium sulphate. It gave a negative Molisch test and it was destroyed by alkali but not by acid. He concluded that the active substance was an albumin.

Dunbar[14] in 1903-11 described the presence of pseudoglobulin, euglobulin, and albumin in pollen and concluded that unless there were proteins present there was no activity.

However, by 1917 the chemical composition of pollen had not been determined and this prompted Heyl[18-23] to make a series of chemical analyses of ragweed pollen. He separated fractions which he called albumin, proteose, and glutelin; and studied the distribution of the amino acids. He showed the presence of pentosans, dextrin, and other substances; and identified the phytosterols of ragweed pollen. He also investigated the coloring substances in ragweed pollen and demonstrated them to be the flavonol pigments, quercetin and isorhamnetin.

Koessler,[27] in 1918, reported on the nitrogen distribution in ragweed pollen extract together with the isolation of amino acids from the protein fraction.

In 1923 Grove and Coca[15] reported work from which they concluded that the active substance in pollen antigen was not protein in character. This work was partially substantiated by the studies of Black.[6] Black later studied the antigenic properties of a substance of carbohydrate nature which he isolated from pollen.[5] This was active when tested on the skin and nasal mucosa of ragweed sensitive patients; however, it contained 6 per cent nitrogen and therefore he was not dealing with a pure carbohydrate but rather a substance containing carbohydrate.

Bernton, Jones, and Csonka,[4,13] in 1925-27, reported the separation of several proteins from timothy and orchard grass pollen and later they reported the isolation of four active proteins from timothy pollen as well as proteose and albumin from ragweed pollen. Caulfeild, Cohen, and Eadie,[12] in 1926, separated the crude extract into a number of fractions whose activity varied. Caulfeild,[10] in 1934-35, separated a carbohydrate

fraction from ragweed pollen which gave a positive scratch test on ragweed sensitive patients and which he used in the treatment of pollen asthma. Caulfeild, Brown, and Waters,[11] in 1935, concluded that there was more than one active substance in the ragweed extract and further that in the serum of a ragweed sensitive person there is more than one specific reagin.

In 1930 Moore, E. E., and Moore, M. B.,[28] studied the distribution of nitrogen in extractions made by various solvents. About the same time Moore, Cromwell, and Moore[29] concluded that giant ragweed and timothy pollen contained at least three distinct antigens.

Johnson and Rappaport,[24] in 1932, fractionated extract of ragweed pollen with ammonium sulphate and concluded that there were at least two fractions present, globulins and albumin. Hechet, Rappaport, and Welker,[17] in 1938, by precipitating at the iso-electric point presumably separated large and small protein like molecules from ragweed pollen.

Harley,[16] in 1937, found that the skin reactive potency of the carbohydrate fraction of timothy pollen is slight. Service,[36] working in the same year, isolated polysaccharides from several western pollens and in contrast to results of Black and Caulfeild found that they did not give skin reactions in sensitive individuals. However, he was able to inhibit analphylaxis in guinea pigs by the administration of the polysaccharide previous to the shocking dose of the antigen.

In 1930 a series of studies was begun by Stull et al., reports of which have appeared from time to time. In 1941 they described the separation of two water soluble antigens from ragweed pollen, Fraction 1 which they considered to have many of the characteristics of a protein; and Fraction 2 which differed markedly from their Fraction 1, not only in a lower nitrogen content but in other properties and reactions.[37] In 1942 they reported a third fraction which differed chemically and immunologically from their Fractions 1 and 2.[38] However, Stull, et al., have given no molecular weight determinations for any of their fractions.

In 1941 Abramson and his co-workers,[1] by means of the Tiselius cell, isolated a "major" antigen and four or more "minor" antigens. Their major antigen had a molecular weight of approximately 5,000 as determined by the sedimentative method. They originally thought that their major fraction (unpigmented fraction) was possibly a polypeptide and contained no carbohydrate; however, in a later article[2] they reported obtaining a qualitative test (Molisch) for carbohydrate and on the basis of chemical reactions they now believe that this fraction is protein like in nature. Their minor fractions, which they designate as pigmented fractions, gave qualitative tests for carbohydrate.

Roth and Nelson,[35] in 1942, described the separation of two fractions from ragweed pollen: one presumably of large molecular size which was responsible for precipitin reactions; the other presumably a small molecule which was responsible for skin reactivity. However, no experimental

data are presented to show the size of the molecules other than the difference in solubilities; namely their so-called large molecule was poorly soluble in distilled water whereas their small size was more readily soluble. But solubility does not necessarily indicate the size of the molecule, for instance, $CaCO_3$ is a small molecule but practically insoluble.

In 1942 Brown and Benotti,[8] using Norite A as an absorption agent for pollen extract, found that it removed a larger amount of non-specific nitrogenous substance than it did of specific and that the nonabsorbed material retained most of the antigenic activity and gave a positive Molisch test. They concluded that the true antigen is not an albumin but a small molecule containing an alpha-amino group and a carbohydrate fraction.

Thus there have been many studies made on the chemical nature of pollen antigen and many conclusions drawn that it is protein or non-protein in nature, still the evidence has been far from convincing as most of it has been based upon presumptive tests. No molecular weight studies were made until those of Abramson. As pointed out by Alles[3] in 1926, the actual isolation of the active antigen as a pure material and the determination of molecular weight with analysis of the elements present are the only absolute criteria of the nature of pollen antigen.

In 1941-42 Rockwell[31,32,33] reported the separation and the therapeutic use of an active antigen from crude ragweed extract as the hydrochloride. This antigen had a minimal molecular weight of 4,453 as determined by its sulphur content. Its nitrogen content was 11.25 per cent; it was levorotary; and an x-ray picture indicated the pollen antigen molecule to be complex. This antigen had many of the properties of a polypeptide and was thought to be loosely combined with some other substance which acted as a hapten or residue antigen.

In 1943 it was shown that the phosphotungstic acid precipitate of crude ragweed extract (which many believe to contain all of the active antigens) contained in addition to nitrogenous substances flavonol pigments and carbohydrates.[34] Also a method was reported which permitted the separation of a major and four other active antigens. It was shown that all of these antigens were flavonol-carbohydrate-peptide complexes which had molecular weights varying from approximately 4500 to 650, a nitrogen content varying from 11.30 per cent to 4.30 per cent, and carbohydrate content varying from approximately 17 per cent to 3 per cent. By this method of fractionation Fraction 1, the major antigen, separated out immediately as the hydrochloride. Further separation was dependent upon permitting the extract to stand in the cold for varying periods of time in the presence of HCl until furfural and methylfurfural formed which indicated that some of the carbohydrate had been destroyed with a resultant change in the solubility of the remaining substance. This means that either these other fractions were combined to each other by means of a carbohydrate which when destroyed liberated the fractions; or possibly that each fraction contained two or more molecules of carbohydrate which

on being reduced to one molecule made the fractions less soluble.

At this time we wish to report further studies on the chemical nature and structure of the major antigen which we have designated as Fraction 1. This fraction we believe is probably the same fraction Stull describes as his Fraction 1 and Abramson describes as his major or unpigmented antigen because the nitrogen content of Stull's Fraction 1 as originally reported agrees with the nitrogen content of our Fraction 1; and the molecular weights of Abramson's major antigen and our Fraction 1 are approximately the same.

### PREPARATION

We have prepared a larger amount of Fraction 1 than before which in turn permitted more extensive purification and analysis.

One hundred grams each of defatted high and low ragweed pollen (1942 crop) were mixed and extracted for twenty-four hours in 2 liters of N/25 NaOH containing 0.5 per cent NaCl. At the end of twenty-four hours the pollen was filtered off and to each 100 ml of clear filtrate was added 7½ ml of concentrated HCl. A precipitate immediately formed which settle out in two hours. The supernatant fluid was decanted and the precipitate centrifuged into a cake. This precipitate was washed with distilled water (all water used in this work was ammonia free distilled water) and then dissolved in 1 liter of distilled water with the aid of a small amount of NaOH. This solution was reprecipitated by adding HCl to bring it to the iso-electric point (pH 3.55). The precipitate was allowed to settle out; the supernatant fluid was decanted; and the precipitate was separated by centrifuging, washed several times and reprecipitated a second time. Finally the precipitate was washed several times, dialyzed against distilled water until the dialyzing solution showed no traces of Cl, frozen and dried in vacuum while frozen using $P_2O_5$ as dehydrating agent. This fraction was whitish in color when acid in reaction and light yellow when alkaline in reaction.

A sample of Fraction 1 was dried to constant weight in a tared crucible in an oven at 103-105° C. and it was found to contain 1.87 per cent $H_2O$; it had an ash of 0.97 per cent, and the chlorine content calculated as $CL^-$ was 3.08 per cent.

Mere reprecipitation is not proof of purity as such a procedure instead of purifying might concentrate the impurity. A compound which leaves a residue (ash) obviously must be impure unless it contains in its molecule a metal or metaloid. Stull's Fraction 1 had a 4.53 per cent ash and his Fraction 1 b had 2.62 per cent ash,[38] whereas our fraction contained only 0.97 per cent ash. Obviously, none of these ashes are consistent with a metal or metaloid being an integral part of the molecule. From this criteria alone it is evident that we are dealing with a purer preparation than was Stull. Furthermore, strong evidence of the purity of this fraction is shown in the determination of its molecular weight by various methods since results which check with each other within limits of experimental

error offer the best possible evidence of the purity of the material analyzed.

### IMMUNOLOGICAL ACTIVITY OF FRACTION 1*

We believe that Fraction 1 is the major active antigen of crude ragweed extract because:

1. It has given a positive skin reaction in every one of well over two hundred cases who gave a positive skin reaction to the crude extract.
2. It has given a positive skin reaction in areas in the skin of non-sensitive individuals which had been passively sensitized with serum from six hay fever cases.
3. Pigs sensitized with crude ragweed pollen extract were given an acute anaphylatic shock when injected with Fraction 1.
4. Pigs sensitized with Fraction 1 had an acute anaphylatic shock when injected with the whole crude ragweed pollen extract.
5. Several hundred patients treated by injection of Fraction 1 have given exceptionally satisfactory therapeutic results.

### ELEMENTARY ANALYSIS AND EMPIRICAL FORMULA

The elementary analysis of Fraction 1 on a moisture, ash, and chlorine free basis is tabulated in Table I. The nitrogen was determined by the micro Kjeldahl method, the sulphur, carbon, and hydrogen by micro

TABLE I. COMPOSITION OF FRACTION 1 ON A MOISTURE, ASH, AND CHLORINE FREE BASIS

| | |
|---|---|
| Nitrogen | 11.92% |
| Sulphur | 0.712% |
| Carbon | 54.56% |
| Hydrogen | 7.82% |
| Oxygen (by difference) | 24.988% |

methods, and the oxygen by difference.[30] All of these determinations were done in duplicate and some were repeated several times.

From the percentage concentration of each element present the number of atoms of each element present in one molecule can be calculated by determining the factor (percentage concentration/ atomic weight) for each element and dividing this factor by the common denominator. This is shown in Table II for all the elements present in Fraction 1.

From the data in Table II we are now able to write the empirical formula for Fraction 1 (major antigen of combined crude ragweed pollen extract). This empirical formula is $C_{205}H_{349}O_{70}N_{38}S_1$

### MOLECULAR WEIGHT

*As Determined by the Empirical Formula.*—On the basis of its empirical formula one molecule of Fraction 1 would contain the elements listed in Table III.

*Since this paper is devoted to the chemical nature of Fraction 1 (major antigen), we are not including details of immunological studies at this time but propose to give them in a separate article.

Thus the molecular weight of Fraction 1 based upon its empirical formula is 4496.084.

The percentage concentration of nitrogen as calculated on its empirical formula is 11.85 per cent which is slightly lower than the 11.92 per cent

TABLE II. CALCULATIONS SHOWING THE NUMBER OF ATOMS OF EACH ELEMENT PRESENT IN ONE MOLECULE OF FRACTION 1

| Element | Percentage Concentration | Atomic Weight | Factor | Common Denominator | Number of Atoms |
|---|---|---|---|---|---|
| Nitrogen | 11.92 | 14.008 | .8509 | .0222 | 38.2 |
| Sulphur | 0.712 | 32.06 | .0222 | .0222 | 1 |
| Carbon | 54.56 | 12 | 4.5466 | .0222 | 204.8 |
| Hydrogen | 7.82 | 1.0078 | 7.7594 | .0222 | 349.5 |
| Oxygen | 24.988 | 16 | 1.5617 | .0222 | 70.3 |

which was obtained experimentally on our present batch of Fraction 1. However, it is almost the same as 11.83 the percentage nitrogen as first reported by Stull for his Fraction 1.[37]

TABLE III

| Element | Grams | Percentage Concentration |
|---|---|---|
| Carbon | 2460 | 54.67% |
| Hydrogen | 351.72 | 7.82% |
| Oxygen | 1120 | 24.915% |
| Nitrogen | 532.304 | 11.85% |
| Sulphur | 32.06 | 0.713 % |
| Total or molecular weight | 4496.084 | |

*As Determined by the Sulphur Content.*—In Table I it is noted that the sulphur content of Fraction 1 is 0.712 per cent. The minimal molecular weight as calculated from this sulphur content would be 32.06/.00712 or 4502.80. The sulphur content which we had reported previously as determined on another batch of Fraction 1 was 0.72 per cent which gave a molecular weight of 4453. These figures check well within experimental error of the determination of sulphur by the micro method.

*As Determined by the Carbohydrate Content.*—As will be discussed in the next section of this paper the carbohydrate present is a pentose which

apparently is arabinose. The pentose concentration of this Fraction, calculated as arabinose, was 3.40 per cent; thus the molecular weight as determined by its arabinose content would be molecular weight of arabinose/concentration of arabinose or 150.08/.034 equals 4414.11. Considering the limitations of the micro method for determining arabinose this is well within experimental error.

Thus we find that the molecular weights of Fraction 1 as determined by elementary analysis, sulphur content, and arabinose content compare very favorably with each other as well as with 5000 the molecular weight determined by Abramson for his major antigen.

### STRUCTURAL ANALYSIS AND FORMULA

As we have previously shown,[32,34] Fraction 1 is a complex containing a flavonol pigment, a carbohydrate, and a nitrogenous substance which had many characteristics of a polypeptide.

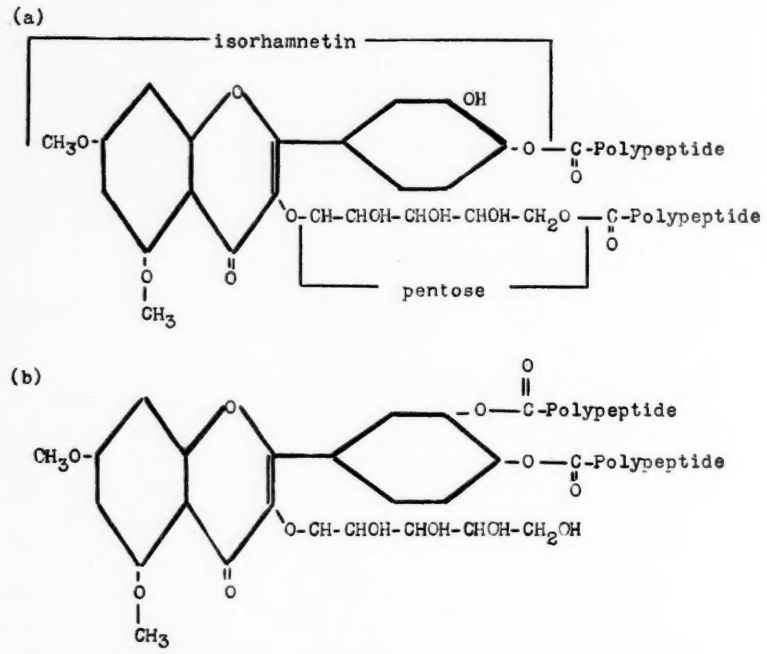
*Flavonol Pigment Component.*—When Fraction 1 is hydrolyzed for one hour with 5 to 10 per cent acid a dark precipitate separates out. We have not been able to isolate a sufficient quantity of this dark precipitate to permit complete analysis, but it contains no nitrogen. We do not know of an accurate quantitative method for the determination of flavonol-pigment. However, in an attempt to obtain some quantitative information the pigment which precipitated out on hydrolysis was filtered through a tared Gooch crucible, washed thoroughly and then dried to constant weight. From this we were able to get the weight of the pigment which separated out and thus calculate the percentage concentration in Fraction 1. This method obviously is not extremely accurate, therefore it was not surprising that we recovered approximately 10 per cent more pigment than could be accounted for if only one molecule of it was present in a molecule of Fraction 1. However, it does indicate definitely that Fraction 1 must contain only one molecule of a flavonol-pigment. Since Heyl has previously shown that the pigments of ragweed extract are quercetin and isorhamnetin,[20] we believe that the pigment in Fraction 1 is isorhamnetin (dimethyl ether of quercetin) as suggested by its purplish color and melting point.

Thus a molecule of Fraction 1 contains one molecule of the flavonol-pigment isorhamnetin.

*Carbohydrate Component.*—The carbohydrate content of Fraction 1 was obtained by a micro adaptation† of a macro method described by Hockett, Guttag, and Smith.[9] Because we had a larger amount of Fraction 1 to work with we were able to distill 100 mg samples from 12 per cent HCl and 10 per cent NaCl. The distillate was precipitated by adding phloroglucinol; it turned yellow then green and upon standing for twenty-four hours a dark bluish black precipitate formed. This color change indicates that the distillate contained furfural and not methyl-

†Details of this method are being described in a separate paper.

**Suggested Formulas for the Major Antigen or Ragweed Pollen**




furfural which yields a reddish brown precipitate. In an earlier work we thought it to be methylfurfural as determined by its action on aniline acetate paper. However, it is furfural; therefore the carbohydrate in Fraction 1 is a pentose (probably arabinose) and not a methylpentose (rhamnose) as we had previously reported.

The amount of carbohydrate present in Fraction 1 on a moisture, ash, and chlorine free basis and calculated as arabinose is 3.40 per cent. With a molecular weight of 4496.084 the percentage concentration of arabinose would have to be 3.33 per cent or some multiple of it, consequently it is obvious from our results that a molecule of Fraction 1 contains only one molecule of arabinose.

*Peptide Component.*—A solution of Fraction 1 was made and the total nitrogen of this solution was determined by the micro Kjeldahl method and the free amino nitrogen was determined by the Van Slyke manometric method. It was found that 5.26 per cent of its total nitrogen content was free alpha-amino nitrogen. Since one molecule contains 38 nitrogen atoms and 5.26 per cent is free alpha-amino nitrogen there must be 1.999 free alpha-amino groups; in other words, there are two free

alpha-amino groups which in turn means that the nitrogenous substance in Fraction 1 consists of two polypeptides and not one.

The above solution after hydrolysis for twenty-four hours with 20 per cent HCl had 74.44 per cent of its total nitrogen as free alpha-amino nitrogen. Since a molecule of Fraction 1 contains 38 nitrogen groups and 74.44 per cent or 28.2 of the amino groups are in the alpha position there must be 28 amino acids in the two polypeptides of which enough must be basic amino acids to account for the other 10 nitrogen atoms. Therefore, there must be from 4 to 10 basic amino acids present.

Fraction 1, therefore, contains two polypeptides whose aggregate number of amino acids is 28, of which 4 to 10 must be basic amino acids. With 70 atoms of oxygen in each molecule of Fraction 1 the only possible way to account for them is that the polypeptides contain a number of dicarboxylic-amino acids.

Thus Fraction 1 (major antigen) is a complex each molecule of which contains one molecule of a flavonol-pigment (isorhamnetin), one molecule of a pentose (arabinose), and two polypeptide molecules. We believe its structural formula to be as depicted in either (a) or (b).

The final proof of this structural formula will be its synthesis. This synthesis because it involves polypeptides is most difficult. However, we are attempting to carry it out and hope to report progress in the not too distant future.

## SUMMARY

1. A simple method is described for the separation and purification of Fraction 1 (major antigen) from crude ragweed pollen extract.

2. The purity of this preparation of Fraction 1 is discussed.

3. The immunological activity of Fraction 1 is briefly given.

4. The elementary analysis of Fraction 1 is given.

5. The empirical formula of Fraction 1 is $C_{205}H_{349}O_{70}N_{38}S_1$.

6. The molecular weight of Fraction 1 is 4496.084.

7. Fraction 1 contains 11.85 per cent nitrogen and 3.33 per cent pentose (calculated as arabinose).

8. Fraction 1 is a complex each molecule of which contains one molecule of flavonol-pigment (isorhamnetin), one molecule of pentose (arabinose), and two polypeptide molecules. The two polypeptides contain an aggregate of 28 amino acids of which 4 to 10 are basic amino acids, and an unusually large percentage of dicarboxylic-amino acids.

9. The suggested structural formula of Fraction 1 is given.

## REFERENCES

1. Abramson, H. A., Moore, D. H., and Gettner, H. H.: An electrophoretically homogeneous component of ragweed producing hay fever. Proc. Soc. Exper. Biol. & Med., **46**:153, 1941.
2. Abramson, H. A., Moore, D. H., and Gettner, H. H.: Electrophoretic and ultracentrifugal analysis of hay-fever-producing component of ragweed pollen extract. J. Physical Chem., **46**:192, 1942.

3. Alles, G. A.: Pollen therapy with protein-free extracts. J.A.M.A., **86**: 1151, 1926.
4. Bernton, H. S., Jones, D. B., and Csonka, F. A.: Pollen proteins and their clinical significance in hay fever. A preliminary communication. South. M.J., **20**:257, 1927.
5. Black, J. H.: A soluble specific carbohydrate of ragweed pollen. J. Allergy, **2**:161, 1931.
6. Black, J. H., and Moore, M. C.: Pollen therapy with protein-free extracts, J.A.M.A., **86**:324, 1926.
7. Blackley, C. H.: Experimental Researches on the Cause and Nature of Catarrhus Aestivus. London: Bailliere, Tindall & Cox, 1873.
8. Brown, E. A., and Benotti, N.: The chemistry of pollen extracts 1. Studies with activated charcoal and ragweed pollen extract. Ohio State M. J., **38**:1011, 1942.
9. Browne, C. A., and Zerban, F. W.: Sugar Analysis, p. 908. New York: John Wiley and Sons, Inc., 1941.
10. Caulfeild, A. H. W.: Preliminary report upon pollen carbohydrate as a therapeutic agent for pollen asthma. J. Allergy, **6**:219, 1935.
11. Caulfeild, A. H. W., Brown, M. H., and Waters, E. T.: Experiments to determine whether the allergically active substance in ragweed pollen is a single entity or multiple. J. Allergy, **7**:1, 1935-36.
12. Caulfeild, A. H. W., Cohen, C., and Eadie, G. S.: The antigenic properties of pollen fractions. J. Immunol., **12**:153, 1926.
13. Csonka, F. A., Bernton, H. S., and Jones, D. B.: Proteins of timothy and orchard grass pollen and their relation to vernal hay fever. Proc. Soc. Exper. Biol. & Med., **23**:14, 1925.
14. Dunbar, W. P.: Quoted by Koessler, K. K.: The specific treatment of hay fever (pollen disease) in Forchheimer's Therapeusis of Internal Diseases, Vol. V, p. 683, New York: D. Appleton & Co., 1914.
15. Grove, E. F., and Coca, A. F.: The nature of the pollen atopen. Proc. Soc. Exper. Biol. & Med., **21**:48, 1923.
16. Harley, D.: Hay fever: The skin-reactive potency of protein and carbohydrate fractions of timothy pollen. Brit. J. Exper. Path., **18**:469, 1937.
17. Hecht, R., Rappaport, B. Z., and Welker, W. H.: Studies on the chemistry and immunology of ragweed-pollen proteins. Proc. Soc. Exper. Biol. & Med., **39**:588, 1938.
18. Heyl, F. W.: Analysis of ragweed pollen. J. Am. Chem. Soc., **39**:1470, 1917.
19. Heyl, F. W.: The protein extract of ragweed pollen. J. Am. Chem. Soc., **41**:670, 1919.
20. Heyl, F. W.: The yellow coloring substances of ragweed pollen. J. Am. Chem. Soc., **41**:1285, 1919.
21. Heyl, F. W.: The phytosterols of ragweed pollen. J. Am. Chem. Soc., **44**:2283, 1922.
22. Heyl, F. W.: Some constituents of ragweed pollen. J. Am. Pharm. A., **12**:669, 1923.
23. Heyl, F. W., and Hopkins, H. H.: The ragweed pollen proteins. J. Am. Chem. Soc., **42**:1738, 1920.
24. Johnson, C. A., and Rappaport, B. Z.: The proteins of ragweed pollens. J. Infect. Dis., **50**:290, 1932.
25. Kamman, O.: Zur Kenntnis des roggen Pollens und des darin erhaltenen Heufiebergiftes. Beitr. z. chem. Physiol. u. Path., **5**:346, 1904.
26. Kammann, O.: Das Heufieber und seine Serumbehandlung. Klin. Wchnschr., **43**:873, 1906.
27. Koessler, J. H.: Studies on pollen and pollen disease. 1. The chemical composition of ragweed pollen. J. Biol. Chem., **35**:415, 1918.
28. Moore, E. E., and Moore, M. B.: Chemical studies on pollen and pollen extracts. 1. Distribution of nitrogen extracted by various solvents. J. Am. Chem. Soc., **52**:3591, 1930.
29. Moore, M. B., Cromwell, H. W., and Moore, E. E.: Studies on pollen and pollen extracts. V. Skin reactions to pollen extracts. J. Allergy, **2**:85, 1930.
30. Niederl, J. B., and Niederl, V.: Micromethods of quantitative organic elementary analysis. New York: John Wiley and Sons, Inc., 1938.
31. Rockwell, G. E.: Preparation of a slowly absorbed pollen antigen. Ohio State M. J., **37**:651, 1941.
32. Rockwell, G. E.: Studies on chemical nature and standardization of pollen antigen. J. Immunol., **43**:259, 1942.

33. Rockwell, G. E.: A clinical study of hay fever therapy with pollen antigen hydrochloride. Ohio State M. J., **38**:433, 1942.
34. Rockwell, G. E.: Active chemical components of crude ragweed extract. Ohio State M. J., 39:128, 1943.
35. Roth, R. R., and Nelson, T.: Proteins of ragweed pollen. J. Allergy, **13**: 283, 1942.
36. Service, W. C.: Antigenic studies of polysaccharides isolated from pollen. Colorado Med., **34**:468, 1937.
37. Stull, A., Sherman, W. B., and Hampton, S. F.: Antigenic fractions in ragweed pollen 1. Water-soluble fractions. J. Allergy, **12**:117, 1941.
38. Stull, A., Sherman, W. B., and Wing, W. M.: Antigenic fractions in ragweed pollen II. Further purification of the water-soluble fractions and a study of alkali-soluble fractions and an estimation of these fractions in pollen extract. J. Allergy, **13**:537, 1942.

## POSSIBLE ETIOLOGY OF APPENDICITIS

*(Continued from Page 26)*

cerning the etiology of the disease is presented which is, at least, as acceptable as other theories now current. The fleeting character of the allergic reaction and its known tendency to subside rapidly, particularly under anesthesia, may explain the sometimes great discrepancy between the clinical symptoms and the gross findings at operation. The involvement of the cecum or other portions of the intestine in the allergic reaction may explain the failure of many patients to be relieved of symptoms at operation. The extreme amount of functional disturbance which may accompany a reversible allergic reaction may explain the discrepancy between clinical symptoms and the actual pathologic change exhibited by the organ. So far as is known, no other explanation than allergy for the local eosinophilia has ever been advanced. And lastly, the allergic picture correlates with the recurrent intermittent development of the disease.

On the whole, then, the conception of appendicitis briefly presented here seems to clarify many of the confusing clinical and pathologic features of the disease, and offers a new viewpoint from which to survey future cases as well as to re-evaluate past experience. Also it offers some hope of prophylaxis.

Before closing, two clarifying points concerning these ideas should be made. First, this discussion does not pertain to symptoms *simulating* appendicitis, but to allergic reactions *leading to* appendicitis. Second, these considerations, even if eventually proven sound and valid, should not change our practice of treating appendicitis as a surgical disease.

# MOLDS AND THEIR RELATION TO ALLERGY

COMMITTEE OF ALLERGISTS FOR THE STUDY OF THE UNKNOWN CAUSES OF HAY FEVER AND ASTHMA

SINCE Van Leeuwen[10] first called attention to molds as a cause of allergic disease, there has been a growing interest in mycology as it applies to clinical allergy.

Although molds are ubiquitous, their relative abundance in different geographic areas varies greatly, hence the relative importance of different fungi as etiologic agents of allergic disease, is local in character. The dominant molds of one locality may be scanty or absent in another. The survey of Bernstein and Feinberg in downtown Chicago showed that 72 per cent of the colonies cultured were composed of Alternaria and Hormodendrum. The Association of Allergists for Mycological Investigation found that 61 per cent of the colonies cultured were of these two species. The latter's survey, including the central area of the United States from the Great Lakes to the Gulf of Mexico, was reported by Morrow, Lowe, and Prince.[7] Other surveys have been reported by Feinberg and Little,[4,5] Durham,[2,3] Prince and Morrow,[8] Schonwald;[9] and others. Wittich[11] has reported, that in addition to culturable fungi, smuts and rusts were etiologic factors in allergic disease in the grain belt of the Great Northwest.

Much coöperative research is still necessary to improve our knowledge of the distribution of molds which may be responsible for allergic disease, to improve our methods of collecting and growing molds, to improve our methods of producing mold extracts, and to purify and biologically standardize these extracts. The following discussion of methods and procedures are based on the observations made by various members of the committee.

## COLLECTION

Air samples were obtained by the use of the Wells air centrifuge. The cellophane slides were forwarded to Dr. W. J. Martin of the Division of Plant Pathology and Botany, Department of Agriculture, the University of Minnesota.

Martin used two methods of isolating single spores of the various fungi present on the slides:

1. The spore was picked directly from the slide by means of a microglass needle manipulated with a modified Chambers micromanipulator (Hanna,[6] Fig. 1); the spore was transferred to a drop of sterile potato-dextrose agar (media drops were on round cover slips placed over small

---

Read in part before the Chicago Society of Allergy, February 15, 1943, by F. W. Wittich.
The Committee of Allergists for the Study of the Unknown Causes of Hay Fever and Asthma was organized to make a systematic study of the possible causes of summer hay fever and asthma of unknown origin. Executive members: Ralph Bowen, Houston, Tex., Chairman; B. G. Efron, New Orleans, La., Secretary; W. H. Browning, Shreveport, La.; Stanley Cohen, New Orleans, La.; Vincent J. Derbes, New Orleans, La.; D. H. Hotchkiss, Houston, Tex.; F. C. Metzger, Tampa, Fla.; Nathan Schaffer, East Orange, N. J.; F. W. Wittich, Minneapolis, Minn.; R. P. Wodehouse, Yonkers, N. Y.

glass cylindrical chambers placed in a sterile petri dish on the bottom of which is a filter paper and allowed to germinate). Fig. 2.

2. The dust from the slides was washed off with sterile distilled water, and dilution plates were made in the regular manner, using potato-dextrose agar.

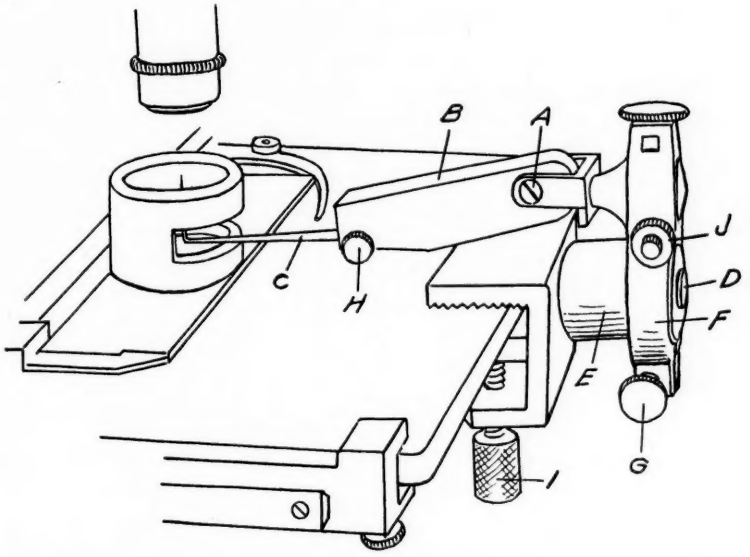



Fig. 1. Apparatus attached to the stage of the microscope. *A*, screw holding wooden arm in position. *B*, wooden arm bearing glass needle *C*. *D*, metal rod projecting from clamp, over which cylindrical piece of wood *E* is fitted. *F*, clamping ring held in place by the screw *G*. *H*, set screw holding glass needle in position. *I*, screw attaching the clamp to the microscope stage. *J*, screw for raising and lowering the needle point. (Courtesy Dr. W. F. Hanna and *Phytopathology*, Science Press Printing Co.)

When sporulation was retarded or would not take place, the cultures were allowed to dry, and then moisture was added to the filter paper. Abundant sporulation frequently followed.

Martin not only isolated the well-known fungi already studied in relation to allergic disease, but also other mold species hitherto unreported in mold surveys. The latter have not yet been identified.

## CULTURE METHODS

Initially the isolates were grown on potato-dextrose agar, and maltose broth. The liquid medium was discarded because it is practically impossible to remove all the broth from the pellicle, and because some mold pellicles are partially immersed in the medium.

*Experiment 1.*—A pellicle of mold produced after three weeks of

growth on maltose broth (10.0 per cent maltose, 1.0 per cent peptone, 0.5 per cent sodium chloride) was suspended so that the broth could drain off of it. It was extracted in 75 c.c. of distilled water, and 67 c.c. of a 1.0 per cent solution (0.67 gram) was obtained. If but 2 c.c. of the broth adhered to the pellicle, the extract contained 0.23 gram of culture medium.

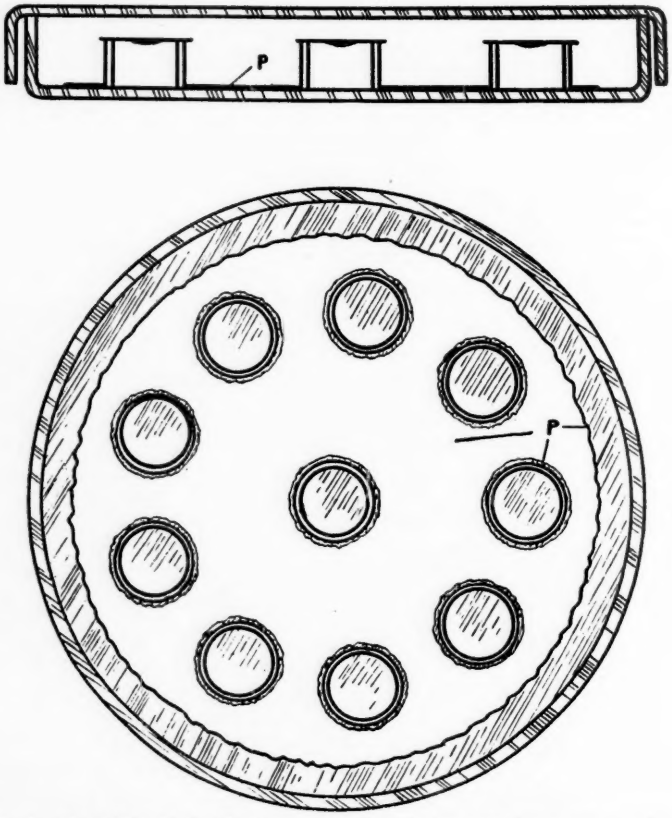



Fig. 2. Petri dish fitted with filter-paper *P*, and ring cells for spore germination. (Courtesy Dr. W. F. Hanna and *Phytopathology*, Science Press Printing Co.)

Thus about one-third of the extract was culture medium constituents; one of which was protein in the form of peptone.

*Experiment 2.*—Inoculation of maltose broth with a mold (tentatively labeled FM 10) produced pellicles which were partially or wholely immersed in the medium. Since the culture medium is an aqueous solution, extraction of the pellicle occurs simultaneously with its growth, and consequently such pellicles contain less antigenic material than those which are not extracted during culture.

The potato-dextrose medium was selected because it is readily prepared,† because it contains a minimum of potentially allergenic material, and because this medium was satisfactory for mold and yeast culture at the University of Minnesota. Isolates transferred to potato-dextrose agar in petri dishes produce pellicles in two to four weeks. The growth is always on the surface of the medium. Practically all the medium can be scraped from the pellicle. If the pellicles are too thin to permit scraping, the medium can be removed from the pellicle after the culture has been dessicated by means of low temperature vacuum distillation.

TABLE I. RESULTS OF EXPERIMENT 4.*

| 1. Defatted Spores | % Protein | % Nitrogen |
|---|---|---|
| Untreated | 23.46 | 3.73 |
| Pressure release | 24.02 | 3.84 |
| Liquid air | 23.72 | 3.80 |
| Waring blender | 24.05 | 3.85 |
| 2. Extracts-aqueous solutions | | |
| Untreated | .0525 | .0084 |
| Pressure release | .0518 | .0083 |
| Liquid air | .0560 | .0090 |
| Waring blender | .0543 | .0087 |

*The nitrogen determinations were made by Dr. Martin W. Sandstrom, Professor Agricultural Biochemistry, University of Minnesota.

## EXTRACTION

The mold pellicles were dessiccated by means of low temperature vacuum distillation. They were extracted at ice box temperature with distilled water for twenty-four to forty-eight hours. Either the Waring blender or a stirrer was utilized to facilitate mixture of the pellicles with the water. Because the specific gravity of mold pellicle is less than that of pollen, relatively large volumes of water were necessary for extraction. With most fungi, 3 grams of pellicle were added to each 100 c.c. of water; with a few it was possible to increase the ratio to 5 grams of pellicle to each 100 c.c. of water.

Between 20 and 30 per cent of the weight of the pellicle is water soluble. This is comparable to the proportion of solids extracted by water from pollens. Boatner and Efron[1] found that 23 per cent (average) of ragweed pollen was water soluble, and 33 per cent (average) of timothy

†300 grams of peeled and sliced potatoes are boiled for fifteen minutes in 1000 c.c. distilled water. To the decanted potato water 10 grams of dextrose and 15 grams of agar are added.

pollen was water extractable. The above finding indicates that the chitinous cell wall of fungi does not interfere with their extraction. Further evidence of this observation are the following experiments:

*Experiment 3.*—Penicillium spores were divided into three lots. One portion was subjected to 2,500 pounds pressure to the square inch. The pressure was then suddenly released, the whole operation taking less than half a minute. The second portion was immersed in liquid air and allowed to thaw very rapidly. The third was agitated in the Waring blender. The mold spores treated by the three methods were extracted with water. The total nitrogen of the extract obtained from the spores treated by the Waring blender was slightly greater than that found in extracts produced by the spores treated by the other two methods.

*Experiment 4.*—The above experiment was repeated with wheat bunt. This smut spore was used because no culture medium or host was present. The results are given in Table I.

It was quite evident that there was no significant difference in the percentages of total and protein nitrogen in the untreated and the disintegrated spores, and in the aqueous extracts obtained from these spores.

## STANDARDIZATION AND PURIFICATION OF EXTRACTS

The committee has been unable as yet to biologically standardize the fungus extracts it has prepared. The reason for this is that the incidence of positive scratch test reactions with these extracts on patients whose symptoms could be attributable to fungi has been small (less than 3 per cent). Since there is no evidence of crossed reactions between various families and genera of molds, and since the positive reactions obtained have not been limited to one genus or family, the total number of positive reactions obtained with a given fungus extract has so far been inadequate for statistical analysis.

Purification methods, which have been applied to house dust, pollens, and other allergens, have not been tried on mold extracts because in order to purify an extract, it is necessary to have sufficient numbers of skin-sensitive individuals on whom the various fractions obtained may be tested by means of scratch tests.

## SKIN TESTS

Scratch tests were performed with 1.0 to 1.7 per cent solutions by weight. Because of the use of relatively large volumes of water for extraction, and because of the necessity of preserving the extracts for a long period of time, the aqueous solutions were first concentrated by means of low temperature vacuum distillation, the solids content of the evaporated extract was determined, and an equal volume of glycerin was then added to the extract. The glycerinated extract was sterilized by filtration through a Seitz filter.

A minimum concentration of 1.0 per cent solution by weight was se-

lected because the proportions of water-soluble constituents in mold pellicles are analogous to those of ragweed and timothy pollens. When 5 grams of ragweed or timothy pollens are extracted in 100 c.c. of water, the concentration of such solutions is between 1.2 and 1.7 per cent by weight (average). Such solutions of pollen extracts produce positive scratch test reactions in a large proportion of sensitive individuals.

Up to the present time, skin tests have been performed with extracts of Penicillium, Aspergillus, Fusarium, Cladosporium, Alternaria, Helminthosporium, Trichoderma, Puccinia graminis, and two as yet unidentified fungi tentatively labeled FM 1 and FM 10.

Positive skin reactions have been obtained with Fusarium, Helminthosporium, Cladosporium, Trichoderma, and Alternaria. In those instances in which positive reactions were obtained with these extracts, the reaction sizes were comparable in every way to those obtained with purified house dust, purified ragweed and purified grass pollen extracts.

Although it is apparent that these molds are not the etiologic agents responsible for "X" hay fever and asthma, further investigation of fungi is justified by the data already obtained.

## SUMMARY

An improved technique for the collection and isolation of air-borne mold spores is presented.

The cultural method used for the growth of mold pellicles is described.

The extraction technique employed by the committee is described.

The results obtained with scratch tests performed with these extracts are presented.

## BIBLIOGRAPHY

1. Boatner, C. H., and Efron, B. G.: Personal communication.
2. Durham, O. C.: Incidence of air-borne fungus Spores. I. Alternaria. J. Allergy, **8**:480, 1937
3. Durham, O. C.: Incidence of air-borne fungus spores. II. Hormodendrum, alternaria, and rust spores. J. Allergy, **10**:40, 1938.
4. Feinberg, S. M., and Little, H. T.: Studies on the relation of microorganisms to allergy. II. Role of yeasts in allergy. J. Allergy, **6**:564, 1935.
5. Feinberg, S. M., and Little, H. T.: Studies on the relation of microorganisms to allergy. III. A year's survey of daily mold spore content of the air. J. Allergy, **7**:149, 1936.
6. Hanna, W. F.: A simple apparatus for isolating single spores. Phytopath., **18**:1017, 1928.
7. Morrow, M. B., Lowe, E. P., and Prince, H. E.: Mold fungi in the etiology of respiratory allergic diseases, I. A. survey of air-borne molds. J. Allergy, **13**:215, 1942.
8. Prince, H. E., and Morrow, M. B.: Molds in the etiology of asthma and hay fever, with special reference to the coastal areas of Texas. South. M. J., **30**:754, 1937.
9. Schonwald, P.: Allergic molds in the Pacific Northwest. J. Allergy, **9**: 175, 1938.
10. Van Leeuwen, W. S.: Allergic diseases in relation to climate. Proc. Roy, Soc. Med., **17**:19, 1924.
11. Wittich, F. W.: Further observations on allergy to smuts. Journal-Lancet, **59**:382, 1939.
12. Wittich, F. W., and Stakman, E. C.: Case of respiratory allergy due to inhalation of grain smuts. J. Allergy, **8**:189, 1937.

# Editorial

## Introduction

"When science comes to a standstill and does not progress in spite of the endeavors of many active men, the blame often lies in the method of presentation, whereby the subject is conventionally considered through an old accepted terminology, to which the majority acquiesce without further questioning, and which thinking men dare to challenge only in isolated instances, and even then with a wee small voice."—GOETHE

WE take pleasure in introducing our first issue of THE ANNALS OF ALLERGY, which appears as the official bimonthly publication of the American College of Allergists.

The American College of Allergists was incorporated as a non-profit organization in November, 1942. The aims and purposes of the College are discussed at greater length in this issue. Included in its many functions is the dissemination of knowledge pertaining to allergy through the medium of a current journal which will contain departments representing all phases of the subject. Its sole aim is to have a professional value for those men who are interested in allergy. For some, such beginnings only excite curiosity and for others, material for dissecting critics. We know it will have a deep sentimental and intrinsic value for the editors, authors, and the publishers.

From those of its readers who are constructively interested, suggestions and criticisms are welcome. Their hearty participation in the enterprise through which they may serve the interests of allergy is cordially invited.

We shall be able to learn of your opinions only through honest and frank comment, which will receive prompt attention. In extending their initial efforts the editors fully appreciate its shortcomings.

Ultimate purposes are threefold. First—to serve that large group of practitioners and specialists interested in applying allergy in their practice and to encourage a large group of the younger men who are already serious, earnest, and enthusiastic workers in allergy. The policy of the publication, therefore, will be liberal and informal in an effort to represent a large proportion of the serious workers in allergy. Second—each issue as it develops will establish departments for articles representing the results of current scientific research, also practical articles on the diagnosis and treatment of allergic states; an abstract department, as well as a listing of current literature pertaining to allergy. At the end of twelve issues an index number will be organized, which we hope in the future may

become an authoritative, permanent reference. There will also be book reviews and an editorial section which will clearly define the policies of the College as the occasion arises. There will be a section for suggestions or ideas for procedure and apparatus; also one for questions and answers. The editorial board is likewise divided into sections which will represent various phases of allergy so that both favorable and unfavorable reports will be published with the realization that the earnest allergist is interested in an unbiased evaluation of these reports. Third—to broaden the scope of allergy so that it may receive proper recognition as a distinct specialty, which will be encountered in the practice of other specialties of medicine and surgery. It is very evident that there is need for such a publication when nearly all the various journals representing the different specialties of medicine contain articles on allergy as applied to their own specialty and show an aroused interest in the subject.

THE ANNALS OF ALLERGY does not in any way intend to encroach upon other publications on the subject any more than do the various existing publications interested in their respective branches of medicine and surgery. The individual physician is becoming more alert and sensitive to the transformations creating his new environment so that he may not become static. Unless medical groups likewise recognize that new conditions require new coöperative methods, they will undergo a slow process of disintegration. Their collective attitudes must be tolerant, depending upon a clear perspective when facing the problems of modern medicine.

---

**Why a College?**

THE American College of Allergists came into existence because of the deep-seated conviction of its founders that a liberal organization, based upon and combining the principles of humility and justice, is needed to fill an important gap in the present structure of allergic affairs. In all sincerity the College invites the coöperation, respect, and support of all those who consider allergy as a specialty, and who share the conviction of its founders that the internist of the future must be, first of all, a master of allergy.

It will be the purpose of the A.C.A. and the ANNALS OF ALLERGY to emphasize and consider numerous phases of allergy heretofore entirely overlooked by other groups. It is hoped, in this connection, that the Central Laboratory for the making of standardized, purified, diagnostic allergenic extracts will eventually be made available to all who wish to make use of its facilities.

Recognizing and upholding reasonable standards, the policy of the A.C.A. is to be, at all times, a liberal and a democratic one, a fact which should prove especially heartening to the younger men interested in this specialty, who need the encouragement that comes with early and fitting recognition.

Elsewhere in THE ANNALS will be found a frank and concise statement of its principles, hopes and purposes, as well as excerpts of its by-laws and other important information regarding the College.

The A.CA. wishes to be helpful, sympathetic and understanding. Its doors are at all times impartially open to all who possess the necessary qualifications to meet its standards and requirements for eligibility to membership. It bespeaks for itself the good will and support of all medical organizations, including existing allergy groups and societies.

F.W.

---

**Appreciation**

Owing to the inclusion of certain information thought necessary in this first issue of the official publication of the College, the editors regret very much having to postpone some excellent articles solicited and submitted until the second number. The editors deeply appreciate the loyal efforts and coöperation which these authors have extended towards making our initial enterprise a success.

We also wish to take this opportunity to express our sincere gratitude to our advertisers who are of much material aid in making the publication possible.

Last, but not least, we take pleasure in thanking the publishers for their keen personal interest in this new venture.

---

## VERNAL CONJUNCTIVITIS

*(Continued from Page 42)*

SUMMARY

1. Vernal conjunctivitis is a component part of ocular allergy.
2. Palliative treatment is not sufficient.
3. Specific treatment with the extracts of the offending pollen will bring quick relief.
4. The dosages of the pollen extracts must be in high concentration for the proper end result.

REFERENCES

Arlt, F.: Prager Vierteljschrft. f. d. Prakt. Heilk., **12**:73, 1846.
Balyeat, R. M., and Bowen, Ralph: Allergic conjunctivitis. South. M. J., **28**: 1005, 1935.
Berens, Conrad: The eye and its diseases. Philadelphia: V. B. Saunders Co., p. 404, 1936.
Duke-Elder, W. S.: Textbook of Ophthalmology. St. Louis: C. V. Mosby Co., **2**:1699, 1938.
Lehrfeld, Louis: Vernal conjunctivitis. J. Allergy., **2**:328, 1931.
Lemoine, Albert: Allergies in ophthalmology. Tr. Am. Acad. Ophth., 198, 1925.
Saemisch, Theodor: Krankheiten der conjunctiva cornea und sklera. G.-S. Handb. d. ges. Augenheilk. **4(1)**:28, 1875.
Townsend, I. F.: Vaccine treatment of vernal conjunctivitis. South. M. J., **16**: 555, 1923.
Thommen, August A.: In Coca, Walzer and Thomman: Asthma and Hay Fever. p. 727, Springfield, Ill.: Charles C. Thomas, 1931.
Weiner, Meyer: Allergic ocular manifestations. South. M. J., **28**:1011, 1935.

# The American College of Allgerists

## AIMS AND PURPOSES OF THE COLLEGE*

The American College of Allergists was incorporated November, 1942, as a non-profit organization. The aims and purposes of the College as set forth in the Charter are:

(a) The establishment of an organization of qualified medical men and scientists of good standing who shall meet from time to time for the purpose of promoting and advancing the study, research and clinical knowledge of allergy as it applies to the various specialties in medicine;
(b) To maintain and advance the highest possible standards among those engaged in the practice of allergy;
(c) To perpetuate the best traditions of medicine and medical ethics;
(d) To establish standards for the qualification, and procedure fort he certification, of men engaged in the specialty of allergy;
(e) To maintain the dignity and efficiency of this specialty in its relation to public welfare;
(f) To promote friendly intercourse among those engaged in the practice of allergy.

The first aim of the College is to act for allergy and allergists, to advance the knowledge and interests of this specialty and to represent the majority of men who are seriously engaged in the solutions of the problems of this field. Since allergy is to be expected in practically every specialty in medicine and surgery, the purpose of the College is to give proper recognition to otolaryngologists and ophthalomologists, pediatricians, dermatologists, gastro-enterologists, as well as the internists who are applying allergy to their practice. Since many of the outstanding contributors are to be found among the immunologists, bacteriologists (mycologists), pharmacologists, biochemists, botanists, plant pathologists, et cetera, these men should receive just recognition by being elected to associate fellowship in the College. All of the fellows in the organization will be physicians practicing allergy and the associate fellows will be composed of the other group just mentioned. The latter's valuable consultation, services and advice will be available at all times when fulfilling the functions and compiling the official publication of the College.

There are over 2000 physicians in the United States and its possessions, Canada, the South American States, and Mexico who are applying and developing the principles of allergic management to their patients. These men represent the various specialties as well as the general practitioner who sees by far the greatest number of allergic diseases.

The College represents a membership larger than any existing allergy society in the United States, and the aims and purposes since the organization has progressed have already mainly been accepted in a comparatively short time, namely:

1. To consider allergy as a specialty which must be correlated with every other specialty of medicine;

2. To give proper recognition to those serious, earnest, and conscientious workers practicing allergy as well as any scientist who has made valuable contributions to our knowledge of allergy;

3. To integrate, harmonize and centralize, without losing the identity or encroaching upon the rights of the various allergy societies in the American states, into a College with a clear perspective of the latter's definition as set forth by the other Colleges for the purpose of establishing certain standards for the practice of allergy;

*The information contained on these pages is available in booklet form to those interested in applying for membership. Applications should be addressed to the Secretary of the College.

4. To standardize methods for the diagnosis and treatment of allergic states by means of a central laboratory for such purposes, as well as a statistical bureau of information on any and all subjects pertaining to allergy;

5. To make possible, through the facilities of certain of its Fellows or the central laboratory, a course for the training and recognition of laboratory technicians in allergic procedures as well as postgraduate studies for any of its members;

6. The dissemination of knowledge pertaining to allergy through the medium of a current journal which will contain departments representing all phases of the subject;

7. The establishment of a Foundation through funds donated by wealthy persons or grateful victims of the disease who are desirous of furthering our knowledge and scope of allergy;

8. The holding of an annual, and later, if possible, sectional meetings, of the College at which the various existing allergy societies would participate for the purpose of presenting articles on scientific research and practical refresher courses on allergy.

A central laboratory has already been established by the College for the making of standardized, diagnostic, allergenic extracts for the exclusive use of its members so that those who avail themselves of this service will be using uniform extracts and therefore get uniform, comparable results, something which has never been attempted before. This central laboratory is run on a cost, coöperative basis and is not attempting to compete with any biologic house. Just as soon as the biologic houses recognize its importance and manufacture antigens standardized and purified and which will meet the requirements of the A.C.A., this function of the College will be discontinued.

The official publication of the College, THE ANNALS OF ALLERGY, is published bimonthly, the first issue being the July-August number, 1943. This is an 80-page magazine devoted to all subjects pertaining to the practice of allergy. A large editorial board conducting the policies of publications by the College includes a staff of corresponding editors from fifteen foreign countries and United States possessions. The board is composed of specialists who have made some personal and noteworthy contributions to the subject as related to their particular fields: internists, pediatricians, dermatologists, otolaryngologists, gastro-enterologists, neurologists, botanists, et cetera.

The subscription price for THE ANNALS is $6.00 per year, which is included in the annual dues.

Since there will be a complete bibliography of publications on allergy and allied subjects, there will be an index published which will provide a permanent reference.

## EXCERPTS FROM BY-LAWS

### Classification of Members

The By-Laws provide for Fellows of four classes:

ARTICLE IV, Section 1.

(a) Honorary Fellows;
(b) Active Fellows;
(c) Associate Fellows;
(d) Corresponding Fellows.

ARTICLE IV, Section 2.

(a) *Honorary Fellows*: Honorary Fellows in the Corporation shall be those who, by reason of personal character, eminence in their practice, meritorious contributions to allergic research, positions of influence and honor, or high attainment in the science of allergy or in the art of medicine, have been recommended by the Committee on Credentials to the Board of Regents for their special and well-earned distinction.

(b) *Active Fellows* shall be members of the medical profession engaged as practitioners, teachers or research workers in the field of allergy, who shall have been elected in accordance with these By-Laws and such additional rules as the Board of Regents may from time to time adopt. . . . .

*Dues.* The fees and first annual dues of the College shall be the sum of $50.00, payable $40.00 thereof on the filing of the application for membership, and the additional sum of $10.00 payable when the Certificate of Membership is issued. Upon rejection of an applicant for failure to meet the requirements of the College, $35.00 of the initial deposit shall be returned.

(c) *Associate Fellows*: Any scientist who has made meritorious contributions to our knowledge of allergy is eligible to membership as an Associate Fellow in the Corporation. He shall have been elected to Associate Fellowship in accordance with these By-Laws and such additional rules as the Board of Regents may from time to time prescribe.

*Dues.* Annual dues for Associate Fellows shall be $10.00 per year, payable in advance.

(d) *Corresponding Fellows*: Corresponding Fellows of the College shall be elected by the Board of Regents under the By-Laws and such rules as the Board may from time to time prescribe, from among the number of contributors on allergy in countries other than the United States, and such selection may be made from residents in the territories and possessions of Canada, South and Central America, Cuba and Mexico.

All those in military service may have their membership fee deferred indefinitely, if desired, but the annual dues are required to defray the current expenses of the College including *The Annals.*

### Qualification of Candidates

ARTICLE IV, Section 4.

(b) A candidate shall be at least twenty-nine years of age and shall have been graduated from a medical school approved by the Council on Medical Education and Hospitals of the American Medical Association.

(c) A candidate shall have been in the active practice of allergy for at least three (3) years preceding his nomination for Fellowship.

(d) The name of each candidate shall be proposed on the official blank of the College.

(e) Additional criteria which may be applied to the Candidate's eligibility for election to Fellowship shall include hospital and academic appointments; personal acceptability by Fellows in his territory, by which he has made his reputation, character, ethical standing and meeting activities; and attendance at one or more of the annual meetings of the College.

(f) Additional criteria which may be applied to a candidate's eligibility for election to Fellowship may include an adequate number of acceptable publications; a thesis on some subject of original investigation; or a reasonable number of clinical case reports which shall be required by the Committee on Credentials. These clinical reports shall be complete in every way with a particular reference to the diagnostic and therapeutic summary in each particular instance.

(h) Election to membership shall require first a two-thirds vote of the Committee on Credentials, and shall then be submitted to the Board of Regents, and shall require a two-thirds vote of the members of the Board of Regents.

(i) Elected candidates shall be notified promptly of their election. Official Fellowship Certificates signed by the Board of Regents shall in each case be issued to an elected Fellow.

### Board of Regents

ARTICLE V, Section 1. *Membership.* The Board of Regents shall consist of ten (10) members, nine (9) of whom shall be elected from and by the Fellows of the College. The first Board of Regents shall be elected at such time and place as the first Board of Directors may determine. Three of said first Board of Regents shall be elected to serve for a one-year term, three shall be elected to serve for a two-year term, and three shall be elected to serve for a three-year term. Thereafter and annually Regents shall be elected to serve for three-year terms.

The Fellows of the College shall at their annual meeting elect one of their number to be President of the College, and the Fellow so elected shall be the tenth member of the Board of Regents.

ARTICLE V, Section 3. *Duties.* The Board of Regents shall have the control and management of the affairs and funds of the College. Without in any way qualifying or limiting such powers of management and control, they shall include the

following: to prescribe additional rules and regulations for the admission of Fellows; to elect Fellows to the College; to arrange for meetings or convocations for the conferring of Fellowship; to arrange for annual, special, and such sectional and other meetings as may be deemed advisable; to create and appoint all standing committees; to create such administrative and executive offices as may be necessary and appoint incumbents thereto; to arrange for printing, editorial work, supervision and publication of the official journal of the College, as well as any annuals or other publications thereof; to elect members of the Executive, Credentials, Judiciary, Biologic Assay, Laboratory, New and Unusual Therapeutics, Program, the Allergy Registry, Finance and other committees; to prescribe additional rules and regulations for the expulsion, resignation or discipline of Fellows; to have general supervision of business affairs and activities of the College; and generally to transact any and all other business of the College not herein otherwise provided for.

**Officers of the College**

ARTICLE V, Section 7. The officers of the College shall consist of a President, a First Vice President and such additional Vice Presidents as the Board of Regents may from time to time determine, and a Secretary and Treasurer. All officers shall be elected by the Fellows of the College at their annual meetings. These officers shall assume their offices upon inauguration on the first day of the annual session next following their election, and they shall serve for a term of one year or until their respective successors are elected and qualified. No officer shall hold office for two consecutive terms except the Secretary and Treasurer.

**Committees**

ARTICLE V, Section 4. *The Credentials Committee.* There shall be a Committee on Credentials selected in such manner and to serve for such periods as the Board of Regents shall from time to time determine. This Committee shall consist of nine members. Three members of the first Credentials Committee shall be elected for a one-year term, three members shall be elected for a two-year term, and three members shall be elected for a three-year term. Thereafter annually new members shall be elected for three-year terms. This Committee shall investigate the qualifications of each candidate for each of the classes of Fellowship. The Credentials Committee shall report its findings as to the qualification of candidates to the Board of Regents, and shall in all instances be subject to the supervision and control of the Board of Regents.

ARTICLE VI, Section 6. *Biologic Assay Committee.* (a) There shall be a Biologic Assay Committee to set up biologic standards for allergenic extracts. These standards shall be the criteria upon which extracts shall be judged in order to determine whether they meet the requirements for allergenic extracts.

(b) This Committee shall also approve or reject extracts submitted to them for approval. Extracts approved by this Committee may be designated "meets American College of Allergists specifications."

(c) This Committee shall do biological analyses on extracts prepared for the Fellows of the College.

ARTICLE VI, Section 9. *The Allergy Registry Committee.* This committee shall determine the nature and character of statistics of the Fellows in the performance of their allergy practice. This committee also is authorized to set up a Bureau of Information based upon information gained by the statistics for dissemination to the members of the College.

**Miscellaneous Provisions**

ARTICLE IX, Section 1. The time and place of the annual meetings of the College shall be designated each year by the Board of Regents.

ARTICLE IX, Section 4. The College may award a material or cash prize to the Fellow making the most noble contribution to allergy during the preceding year. The Awards Committee consisting of three members appointed by the Board of Regents shall present the same. Funds for awards shall be voted from the general funds of the College. No Fellow shall be awarded such distinction more than once.

ARTICLE IX, Section 5. The annual dues shall be fixed by the Board of Regents, but shall not exceed $12.00. The non-payment of dues for three consecutive years shall be deemed to constitute a forfeiture of Fellowship.

*(College News Continued on Page 89)*

# Suggestions and New Procedures

## PRACTICAL SUGGESTIONS FOR CLEANING AND STERILIZING NEW AND USED GLASSWARE FOR ALLERGENIC EXTRACTS

Most textbooks on allergy are replete with explicit directions for the preparation and standardization of allergenic extracts, but neglect the important detail of emphasizing the absolute necessity of properly preparing the tools with which these extracts are handled. The best standardized extracts become worthless, especially for skin testing, when the glassware becomes contaminated with numerous potent antigens and not adequately removed. This undoubtedly accounts for a certain number of numerous positive reactions on endermal testing which are false and attributed to other factors. This observance does not apply to most of the larger allergy clinics where such precautions are routinely taken. Many men who do not appreciate the importance of this detail, have recently commenced to apply allergy to their practice, and are making their own extracts.

Small et al. (J. Allergy **13**:380, 1942) emphasize the importance of contamination, especially when some skins are so sensitive that it is fairly common for patients to react to 1:1,000,000 extracts and may react to a 1:1,000,000,000 extract. Other observers have shown that allergenic extracts are not thermolabile and that sufficient extract may be absorbed by the glass syringes and produce false reactions on highly sensitive individuals. Allergens may form films on glass or metal, and may not be removed by rinsing or destroyed by ordinary sterilization methods.

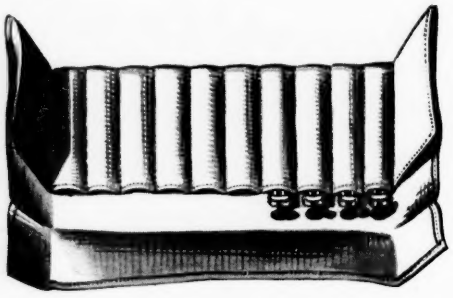
It was shown that cleaning syringes containing allergens by rinsing several times in distilled water and boiling in clean tap water and allowing them to cool between sterile towels, which is the custom of many allergists, is not sufficient to prevent contamination and false reactions. These observers made carefully controlled experiments and presented a safe method of preparing syringes, needles and bottles. Essentially this consisted of immersing over night the plunger and barrel of the syringes in commercial sulfuric acid containing 2.5 per cent sodium bichromate, rinsed in tap water and then in distilled water. Needles were boiled ten minutes in 1 per cent trisodium phosphate solution, then held thirty minutes, reboiled, rinsed in tap water, and brought to a boil in dilute Ph. 6.0 phosphate buffer, in which they were allowed to remain over night. They were then rinsed in distilled water, placed in clean towels and steam sterilized.

Bottles were immersed in 1 per cent trisodium phosphate solution, boiled ten minutes, allowed to cool one hour, reboiled, rinsed once in decinormal hydrochloric acid solution, then four times in hot tap water with a final rinsing in distilled water, and after draining, were sterilized by dry heat for two hours at 160° C.

The procedure which we have been using for the past six years and found satisfactory is as follows:

New glassware is cleansed with a brush in a warm 1 per cent solution of anhydrous tetrasodium pyrophosphate ($NA_4P_2O_7$), which has a pH of 10.2, is then rinsed under cold running tap water several times, and is immersed for a couple of hours in a very dilute solution of hydrochloric acid (N/10 or about 8-10 c.c. of C. P. hydrochloric acid to the liter). It is then rinsed thoroughly first with tap water then with distilled water. Bottles are inverted in wire baskets, allowed to stand until partially dry and placed in an ordinary detached oven used with a gas stove; gradually they are heated to 500° F and sterilized at that temperature for one hour.

Used rubber stoppers or caps are prepared by washing in running tap water and autoclaved at 15 pounds pressure for twenty minutes, rinsed in distilled water, drained and immersed in 4 per cent phenol for at least twenty minutes. The baskets containing the sterilized bottles are placed on a sterile towel upon which is a layer of sterile gauze (to prevent lint). While still hot the bottle is grasped with



INDIVIDUAL POCKETS WITH STERILE SYRINGES.
(DUCK MATERIAL WHICH CAN BE FOLDED INTO PACKETS FOR AUTOCLAVING)

a sterile towel and the mouth flamed. The stopper in the phenol solution is grasped with a flamed forceps, plunged into boiling distilled water, excess water shaken off and then passed swiftly through the gas flame and carefully inserted into the bottle.

*Syringes.*—The plungers and barrels are rinsed thoroughly in very hot running tap water, immersed in a pan containing 1 per cent anhydrous tetrasodium pyrophosphate. A wooden applicator with a cotton swab is used to cleanse the inside of the barrels. They are rinsed under cool running tap water several times, and immersed in acidulated water (N/10 HCL.) over night. In the morning they are rinsed with tap water then with distilled water, and are placed in series of ten in a special container made of heavy duck so that each syringe will be in a separate pocket with plunger in the barrel (Fig. 1). Side and top flaps are folded in and made into a neat packet and wrapped in a clean towel, and autoclaved in an ordinary aluminum pressure cooker at 20 pounds pressure for one-half hour.

*Needles.*—Needles are rinsed in hot running tap water, then boiled in 1 per cent anhydrous tetrasodium pyrophosphate solution for five minutes, rinsed in distilled water, placed in clean towels, steam sterilized and dried by blowing air through them, and boiled in distilled water just before using.

*Seitz Filters.*—The perforated rubber stopper is removed from filter, and both are washed in hot running water with a brush. Both are autoclaved at 15 pounds pressure for twenty minutes; the filter is scrubbed with 1 per cent anhydrous tetrasodium pyrophosphate solution, rinsed in running tap water, then in distilled water, dried thoroughly, and the disk and pad are replaced. The filter is then wrapped in two towels, tied with string, and is placed inverted in wire baskets and heated in the oven at 350° F. for one hour.

FRED W. WITTICH, M.D.

# Abstracts

## PROGRESS IN ALLERGY

Physicians associated with the field of allergy are, of course, familiar with the papers published in this and other journals devoted to the subject. In addition, each of the journals publishes selected abstracts of such papers as are interesting to its readers, although originally printed elsewhere. Every year the excellent reviews by Rackemann, Smyth, Weber, and others, evaluate the more important work of the preceding twelve months.

It is not in any sense the purpose of these columns to compete with other such services, some of which could not possibly be excelled. It is rather an attempt to furnish a critical analysis which will serve three different and distinct purposes. Fulfilling some of the functions of the annual reviews, it will differ from them in being published at intervals of two months instead of twelve or more. It will tend to focus attention upon the most recent of the more important trends in the advancement of the specialty, and yet will look further afield, bringing to its readers knowledge of work in allergy, no matter where practiced or by whom. Such work will be chosen for comment because it is distinguished by its potentialities rather than by its immediate importance, or, because of its interest rather than its gravity. Lastly, although current in scope, it will not limit itself to the discussion of current literature but rather, whenever pertinent, will comment upon previous work related to the same subjects.

Occasionally, when a number of papers on a single phase of allergy are available for discussion, all, if possible, will be correlated at one time. In any case, no review in any issue will necessarily be complete in itself, but instead, from issue to issue, will furnish a continuous commentary so written that he who runs may read.

Workers in any of the fields of anaphylaxis, atopy, or allergy, or their related subjects, are invited to send reprints or abstracts for consideration in these columns. Since papers, as published, are rarely in their final or permanent form, authors are invited to add to their papers any new material they may have acquired after publication. In the same way, comments are invited by the original authors, or others, whose papers have been abstracted or reviewed.

As with the passage of time, the knowledge of Allergy increases among physicians and laymen, the list of known allergens lengthens. Weber's[26] monumental work on the external causes of dermatitis, as published at varying intervals in the *Archives of Dermatology and Syphilology,* listed the causes of contact dermatitis alphabetically by individual substances, and also as associated with each important occupation. This list should be within reach of any allergist who sees cases of this type. The list is doubly useful, since it includes also the table of irritating plants as compiled by the Bureau of Plant Industry of the Department of Agriculture. There is no similar list available for the known atopens. In any case, for all phases of allergy an abstract review must, of necessity, give prominence to reports of such substances, listing them as soon as possible.

Harris[8] adds to the known causes of contact dermatitis. The patient's eyelids were affected by philodendron (Scandens Cardatum). Philodendron is a common house plant, and other cases will undoubtedly be reported upon, as its potentialities for acting as a dermatological irritant are more widely known.

Markson[13] found eight cases of dermatitis involving the dorsum of the hands and arms, all of which were due to oil from Brazil nuts. The patients, all women,

worked with candy. Patch tests with Brazil nut oil were positive in all but one case

Cod liver oil is becoming more and more commonly prescribed in ointments for the treatment of chronic skin conditions. Cope[1] describes a patient who had varicose ulcers which were treated with an ointment of this composition. There was a resulting acute vesicular dermatitis. The individual ingredients of the ointment gave negative patch tests, excepting for the cod liver oil which was strongly positive. It was considered the causal substance and, therefore, reported upon.

As early as 1908, Lewin[10] described morphine as a cause of contact dermatitis. Palmer[18] brings to our attention a patient who had a skin condition localized to the cubital fossæ, neck, postauricular regions, eyelids, and fingers. Patch tests with solutions of the 1:1000 dilution of codeine, morphine, ethylmorphine, and diacetylmorphine were all found to be positive. This patient is singled out for comment because codeine taken by mouth by the same patient, caused urticaria. Drug sensitivity is still the lease explored aspect of allergy, and it would be interesting to speculate on the various immunological relationships involved in a case in which the substance caused two such divergent conditions by two such differing mechanisms.

This is seen again in another aspect, in a paper by McAlpin and Berens.[11] Pontocaine, rarely considered a cause of contact dermatitis, and accepted among the safest anesthetic agents for the eyes, affected four of their patients. These patients had a pontocaine dermatitis of the fingers, three presenting an associated blepharoconjunctivitis. All of the patients gave positive patch tests. One of them, however, gave a positive conjunctival test. If the blepharoconjunctivitis was a contact type of dermatitis, one would expect none of the patients to give a conjunctival test. Its presence suggests a relationship between two types of conditions and tests not at present considered similar.

Soap dermatitis has been reported upon by many workers Patch tests with soaps, as is generally known, are notoriously difficult to evaluate, because even the most nearly neutral soaps will, in concentrated solution (or in dilute solution given sufficient time) cause a local reaction on apparently normal skin. Especially interesting for this reason is Hailey's[7] description of a patient who had a dermatitis on the finger whenever soap became adherent to her platinum ring. If the ring was cleaned after washing, there was, however, no eruption, evidently exonerating the metal as a cause. He also reports that patch tests with the soap were negative, not directly incriminating the soap. If we accept, as we must, the fact that a metal which reacts on few skins can, when associated with a substance which causes positive patch tests in many normal individuals, cause an eruption, although the patch tests of both substances are described as negative, we are faced with this possibility. In cases of contact dermatitis it would not be sufficient to test with each individual ingredient, since if the tests were negative, each negative ingredient would, of necessity, have to be used in conjunction with every other negative ingredient for a further series of tests. Under such circumstances, the negative patch tests to the single ingredient would have little meaning, and the difficulty in uncovering a contact factor would be incredible. It would seem that further tests of the original patient would offer a more acceptable working hypothesis.

In another sphere of allergy, Derbes[3] brings to our attention a case of seasonal hay fever and asthma, both due to narcissus bulbs. Skin tests made with an extract of the bulbs were positive, both by direct test and by passive transfer. The direct tests caused a severe constitutional reaction. The patient, a farmer, reacted to the biologically related substances, onion, garlic, asparagus, and orris root. Extracts of the flower which gave no positive tests supported the assumption that the flower itself was not the cause of the symptoms.

When the treatment of epidermophytosis with phenol and camphor was first

introduced, it was immediately suspected, since both these substances were potent allergens, that there would be a large number of cases of contact dermatitis. Miller[14] gives us the details of a death following treatment with a mixture containing one ounce of camphor and four ounces of phenol. The patient, an eighteen-year-old lumberman, had a skin condition involving the shoulders, arm, and trunk. The first application of the phenol-camphor mixture caused burning and dizziness. The mixture was diluted but when reapplied, it was immediately followed by extreme dyspnea, death occurring within fifteen minutes. Postmortem studies gave the cause of death as an acute pulmonary edema. Chemical analyses revealed the presence of phenol in the stomach, heart, spleen, and kidneys.

Diethylstilbestrol has been reported as causing a number of untoward reactions, including angioneurotic edema and exfoliative dermatitis. The former of these, reported by Saphir and Weinglass,[21] occurred in a woman who received daily, for the relief of menopausal symptoms, half a milligram of diethylstilbestrol. The fifth day following the injections, edema of both hands appeared, and by the seventh day, a laryngeal stridor accompanied by an angioneurotic edema of the face and neck. The fact that the substance caused an angioneurotic edema is not as important as the remainder of the report, which states that intradermal tests with 0.1 c.c. of a 1:2000 dilution of the substance, gave positive tests as shown by wheals and pseudopodia with a surrounding flare. It is reported that these tests did not appear, however, for several hours. It would seem, therefore, from this report, that in this patient, the tests with stilbestrol, although not occurring for several hours, were of the type usually associated with an immediate reaction.

In the latter case, as reported by Kasselberg,[9] the patient who had received intramuscular injections of the material once a week for three weeks suffered from a generalized exfoliative dermatitis. Here again the condition is not as interesting as the report of the tests. Patients suffering from exfoliative dermatitis have, on rare occasions, been reported as giving positive skin tests to the drugs to which they were sensitive. In this patient, the material was diethylstilbestrol, but scratch tests gave strong reactions with wheals, pseudopodia, and a surrounding flare within twenty minutes. The full potentialities and strange behavior of diethylstilbestrol are not as yet fully known, and studies in this direction would seem to be indicated.

Diodrast has frequently been described as a cause of untoward reactions. Goldburgh and Baer[5] describe the death of a female patient who had had an intravenous urogram, followed seven days later by a mild attack of asthma, the first of which the patient had suffered for many years. Preceding a second intravenous urogram, a few drops of diodrast were placed under the tongue. This did not react, and the dye was, therefore, administered intravenously. Five minutes following the completion of the injection, the patient became cyanotic and convulsed, and within twenty minutes, died. The authors suggest that patients be questioned for previous history of iodine sensitivity and for evidence of bronchial asthma. They feel that tests with a small quantity of diodrast placed under the tongue should be performed on all patients who undergo intravenous urograms. In the absence of symptoms, there are no contraindications to using the drug by the intravenous method.

Naderman and Robbins,[16] however, much impressed by the fact that untoward reactions, such as urticaria and bronchial asthma, frequently follow intravenous diodrast, performed skin tests on 404 patients. Of these, 323 had manifested no general reaction, while eighty-one had experienced undesirable effects. Of the larger group 72.8 per cent gave negative skin tests. In the second group, 82.8 per cent showed positive skin tests. Naterman suggests that all patients to whom diodrast is to be administered be skin tested to the material, using 0.05 ml. of the undiluted substance. He feels that general reactions may be expected in those patients whose skin test wheal is larger than 15 mm.

Vance and Strassman,[25] following the performance of autopsies upon seven patients who had been given injections of foreign protein, make a rather pertinent observation. One patient died following intradermal testing with a mixture of silkworm, wool, and kapok extracts, while another had had an injection of ragweed extract in the course of treatment. The remaining patients had received horse serum. All showed the typical postmortem findings, the usual bronchial spasm, cerebral and laryngeal edema, and eosinophilia in the bronchial mucosa It is worth noting that the authors found a very striking resemblance in the findings between the asthmatic and presumably nonasthmatic patients.

Simon[23] has previously reported upon sensitivity to mammalian sera and now adds to his previous report with four additional patients who had multiple sensitivities, among others, to horse, cow, dog, guinea pig, hog, rabbit, sheep, cat, and porpoise. Studies by the passive transfer method showed that each patient had one particular mammalian serum which neutralized the reagins for all the mammalian sera, whereas the other sera neutralized the antibodies for themselves alone, or for themselves in addition to one or several others, but not for all. In one patient, this serum was horse serum, in a second, sheep, and in two others, dog serum. Simon believes, therefore, that serum-hypersensitivity is only partially species-specific, and the reagins for any one particular mammalian serum which the patient carries, many vary from patient to patient as far as its neutralization capacities are concerned. The work suggests that there is a fertile field for investigation in the multiple common allergenic determinants in mammalian sera as well as in the multiple neutralizing components in the patients' reaginic sera.

Infection of the nasal sinuses at various times has been considered responsible for diseases in many organs in different parts of the body. Shannon[22] states that he has observed a close connection between infection of the nasal sinuses and "dissociated albuminuria," feeling that the relationship is so close that nasal sinusitis should always be suspected whenever, in the absence of other kidney disease, albuminuria is found. He states that in such patients, morning specimens collected before arising are invarably albumin-free, while daytime urines contain albumin. Successful treatment of the infection is followed by the complete disappearance of the urine albumin.

Since nasal sinusitis is comparatively common, and albuminuria rare, it is not at all surprising that the physician who treats cases of albuminuria will find among them a large number of patients who have sinusitis. In our own public and private clinics, the opposite side of the picture is seen. Nasal sinusitis, as diagnosed by the otolaryngologist, is fairly common, but albuminuria is comparatively rare. Since the relationship does not hold true in both groups of patients, it would seem that other factors must have intervened in the group of patients upon whom the studies were done. When a causal relationship between two different conditions is suspected, corroboration must come from the expert treating both conditions, and the mathematical ratios must be such as to be statistically acceptable.

A similar observation has been made regarding reports of pulmonary fungus infections. Such reports are fairly common, and yet almost none has been made by allergists, who, in the aggregate, see tens of thousands of patients with chest conditions. Hankin[19] reports upon two cases of acute pulmonary moniliasis, both confirmed by positive blood cultures. The first of these responded to sulfanilamide, and was symptom-free for one and a half years following his discharge from the hospital The second patient, who received sulfapyridine, suffered a uremic reaction and died. Reeves[20] reports upon three cases of pulmonary fungus infection, treated by "desensitization" with a vaccine obtained by washing the slant culture in normal saline and killing the organisms in the filtrate. Following such "desensitization," the patients were given potassium iodide therapy and in some cases ethyl iodide inhalations. The three patients all recovered and remained well.

Pulmonary moniliasis and also gastro-intestinal moniliasis are probably much more common than is generally supposed. In 1934 Oliver[17] published a work entitled "The Etiology and Treatment of Spasmodic Bronchial Asthma." His findings were based upon fifty cases of bronchial asthma, in all of whom the cultures of the sputum showed the presence of monilia. The patients were all treated with massive doses of potassium iodide, and within a comparatively short period of time were all greatly improved, if not completely cured. Since potassium iodide is one of the treatments of choice for many pulmonary affections, one wonders how many patients in the intrinsic group of bronchial asthma sufferers are really receiving treatment for a pulmonary fungus infection, rather than for their bronchial asthma.

The chemistry of the skin in allergic dermatoses continues to be a fruitful field for study. Engman and MacCardle[4] report the histologic, spectrographic, and micro-incineration of the skin in disseminated neurodermatitis and state that there is a general and a local cutaneous magnesium deficiency. Various sections of the skin show important differences. The spinous cells in the active lesion seem to have been deficient in calcium and magnesium, while the epidermis as a whole seems to be deficient in intranuclear silicon. Albino rats, when given diets deficient in magnesium, developed dermatologic lesions similar to those seen in neurodermatitis. The authors feel, therefore, that magnesium deficiency causes a physical-chemical change in the proteins of the epidermis, so that the calcium and silicon which are biologically necessary to the integrity of the skin are no longer retained.

Cornblett, Ingraham, and Schorr[2] demonstrated that in and around the area of a wheal, the sodium concentration is reduced. The administration of sodium lowers the sodium content of the wheal still further, there being at the same time a diminution of the calcium in the blood. The authors feel that the skin of eczematous patients needs more potassium than normal. Eczema patients when given potassium chloride did not, however, improve Eleven patients with chronic urticaria when given the same treatment resulted in the complete relief of two, and the improvement of two more. Urticaria, however, is so capricious a condition that improvement or relief of four out of eleven patients would not seem to indicate that potassium chloride is the specific therapy for which urticaria patients have long been waiting.

Drug therapy in the treatment of migraine is discussed in detail by Trowbridge, Von Storch, and Moore.[24] In this excellent review, the authors analyze the effect of a number of drugs upon two hundred patients. The drugs are classified as vasoconstrictors, narcotics, barbiturates, analgesics, bromides, endocrines, and drugs directly affecting the gastro-intestinal tract (as hydrochloric acid, sodium bicarbonate, and Seidlitz powders). In their series, ergotamine tartrate caused complete relief in 80 per cent of the patients. Morphia was effective in only 50 per cent of the patients, while phenobarbital and acetylsalicylic acid helped respectively in 16 per cent and 10 per cent. All of the other drugs, which included caffeine, pantapon, codeine, scopolamine, phentobarbital, allanol, acetanilid, amidoyprine, phenacetin, and various endocrine preparations, were realtively ineffective, although the best effects were obtained with the vasoconstrictor types of medication. The patients were evidently not analyzed from the point of view of possible allergy.

Gottlieb,[6] assuming that the immediate cause of migraine was a local arterial change, which might be either spasm or dilatation, used amphetamine for therapeusis. Given intravenously it quickly aborted attacks in twelve out of eighteen patients. Eight patients in a group of twenty-two felt that amphetamine gave relief when taken orally during the prodromal stage of their condition. It was found, however, that only those patients in whom intravenous injection was successful were benefited by oral administration. Withdrawal of the drug resulted in the recurrence of symptoms. It is difficult to judge the exact action of amphetamine. When a condition in which psychological factors are so important is treated

with a drug which is noted for its effects upon the psyche, the pharmaco-dynamic action of the same drug must, of necessity, be secondary. Amphetamine would nevertheless appear to be another type of medication to be added to the long list of those used in the treatment of migraine.

For those asthmatic patients who become epinephrine-fast, Maietta[12] advocates the use of an intramuscular injection of a mixture of equal parts of ether and peanut oil, the dose consisting of 2 ml. He states that the immediate effects are transient and unimportant, although the taste and smell of ether may be perceived soon after the injection and last as long as one day. There may be a temporary burning sensation at the site of the injection, but within a few hours, the patient becomes quiet and is breathing easier The ether, excreted by the bronchial mucosa, has an expectorant action. The dose may be repeated, if necessary, every few hours. What treatment can be given to the patient while he waits for the ether in oil to take effect is not indicated.

Epinephrine in oil or in gelatin, although noteworthy additions to the armamentarium of the allergist, both have their obvious drawbacks. Naterman[15] reports a notable advance in this type of therapy. When epinephrine base is placed in a solution of sodium thioglycolate, oxidation is prevented so that the suspension is stable for as long as fifteen months. Following injection, its absorption is so slow that no epinephrine side-effects are recorded, although three to four times the usual quantity of epinephrine may be administered. The relief is reported to be long lasting, and the preparation superior to the oil suspension, since it is easier to administer, causes less local reaction, and is equally as effective as the preparations of this type previously reviewed.

REFERENCES


1. Cope, E. P.: Contact dermatitis due to cod liver oil: Report of a case. Arch. Dermat. & Syph., **46**:140, 1942.
2. Cornblett, T., Ingraham, R. C., and Schorr, H. D.: Calcium, potassium, and sodium metabolism of the skin. Arch. Dermat. & Syph., **46**:833, 1942.
3. Derbes, V. J.: Occupational, seasonal hay fever and asthma due to narcissus bulbs. South. M. J., **35**:912, 1942.
4. Engman, M. F., Jr., and MacCardle, R. C.: A new approach to the problem of a disseminated neurodermatitis. Arch. Dermat. & Syph., **46**:337, 1942.
5. Goldburgh, H. L., and Baer, S.: Death following the intravenous administration of diodrast. J.A.M.A., **118**:1051, 1942.
6. Gottlieb, J. S.: Effect of benzedrine sulphate on migraine. Am. J. M. Sc., **204**:553, 1942.
7. Hailey, H.: Dermatitis from soap adherent to a platinum ring. Arch. Dermat. & Syph., **46**:285, 1942.
8. Harris, J. H.: Dermatitis of the eyelids due to philodendron 'Scandens Cardatum" plants. Arch. Dermat. & Syph., **45**:1066, 1942.
9. Kasselberg, L. A.: Case of exfoliative dermatitis due to diethylstilbestrol. J.A.M.A., **120**: 117, 1942.
10. Lewin, L.: Die Gewerbliche Vergiftung der Haut durch Morphine und Opium. Med. Klin., **4**:1633, 1908.
11. McAlpine, P. T., and Berens, C.: Allergic dermatitis and blepharoconjunctivitis caused by pontocaine. Am. J. Ophthal., **25**:206, 1942.
12. Maietta, A. L.: The use of ether in oil intramuscularly in the traetment of bronchial asthma. New England J. Med., **227**:985, 1942.
13. Markson, L. S.: Dermatitis from seed and oil of Bertholletia Excella (Brazil nut). Arch. Dermat. & Syph., **46**:831, 1942.
14. Miller, F. G.: Poisoning by phenol (used in the treatment of ringworm). Canad. M. A. J., **46**:615, (June) 1942.
15. Naterman, H. L.: Adrenalin base suspended in an aqueous solution of sodium thioglycolate in the treatment of asthma. Northeast J. Med., **227**:736, 1942.
16. Naterman, H., and Robbins, S.: Cutaneous tests with diodrast to predict systemic reactions, J.A.M.A., **119**:491, 1942.
17. Oliver, H. Gordon: The Etiology and Treatment of Spasmodic Bronchial Asthma. London: H. K. Lewis Co., 1934.
18. Palmer, R. B.: Contact dermatitis due to codeine. Arch. Dermat. & Syph., **46**:82, 1942.
19. Hankin, Morris A.: Pulmonary moniliasis. Connecticut M. J., **6**:264, (April) 1942.
20. Reeves, Robert J.: The diagnosis and treatment of pulmonary fungus infections. J. Tennessee M. A., **35**:207, (June) 1942.
21. Saphir, W., and Weinglass, A. R.: Severe angioneurotic edema following diethylstilbestrol therapy. J.A.M.A., **119**:567, 1942.
22. Shannon, W. Ray: Nasal sinusitis and orthostatic albuminuria in childhood. Minnesota Med., **25**:458, 1942.
23. Simon, F. A.: Human allergy to mammalian sera. J. Exper. Med., **75**:315, 1942.
24. Trowbridge, L. S., Von Storch, T. J. C., and Moore, M.: The drug therapy of migraine headache. New England J. Med., **227**:699, 1942.
25. Vance, B. M., and Strassman, G.: Sudden death following injection of foreign protein. Arch. Path., **34**:849, 1942.
26. Weber, L. F.: External causes of dermatitis, a list of irritants. Arch. Dermat. & Syph., **35**:129, 1937.

# Questions and Answers

**What are the indications and methods of treatment with histamine?**

Histamine therapy has been used in the treatment of cold allergy where patients show allergic symptoms when exposed to cold temperatures; of allergic reactions to insulin, asthma and hay fever; chronic or recurrent urticaria; angioneurotic edema; Ménière's disease; histamine headaches which include "histaminic cephalgia" and allergic headaches.

Although histamine is highly toxic when first injected in comparatively small amounts (0.3 mg. subcutaneously) in the allergic and nearly as much in the nonallergic patient, closely repeated subsequent injections produce a tolerance to histamine in direct ratio to the frequency and speed of injections. Whether this is an increased tolerance or a desensitization process implies an antigen-antibody reaction from evidence at hand. Doubtful but certainly repeated injections of the drug alters the physiology of the organism in some way so as to diminish or abolish the pathologic condition. The basis of this state of altered responses of the body to histamine is not yet understood.

Several methods of successful treament of allergic states with histamine are used. Fiessinger and Gajdos (1935) reported the successful treatment of intractable urticaria by ionization with histamine. An aluminum plate connected with the positive electrode of the galvanic current was placed upon a compress moistened with 1:10,000 aqueous histamine hydrochloride placed over the epigastrium and 6 to 10 milliamperes passed through the circuit from five to ten minutes while the patient held the indifferent electrode in the hand. Marked relief was reported after a score of such treatments.

Alexander modifies the technique by using an electrode 2 or 3 inches square to which is attached cotton or blotting paper saturated with 1:10,000 histamine diphosphate. This is placed on the skin of the upper abdomen and attached to a "B" battery. The patient holds the indifferent electrode in his hand, 2 ma. are run through the circuit for two minutes. When histamine is driven by the current into the skin a large wheal the size of the positive electrode appears on the skin. The histamine deposited as such remains in the skin for several days and is slowly absorbed.

Alexander and Elliott reported at a meeting of the Central Society for Clinical Research (Chicago, November 3 and 4, 1939) the beneficial results in the treatment of chronic urticaria by the intravenous administration of histamine. They believed that this method was an improvement over the slower subcutaneous method. They stressed certain precautions to be used in order to avoid histamine shock, but indicated the extremely rapid tolerance acquired by the organism for histamine to rapidly repeated increasing doses based on the amount that would produce undesirable mild symptoms such as a feeling of warmth and face flushing. By experience they recommended the initial dose of 0.2 mg. of histamine diphosphate (0.2 c.c. of a 1:1000 dilution) diluted to 20 c.c. with physiologic saline solution. A No. 24-gauge needle is used and the histamine solution injected intravenously intermittently. 1 c.c. is very slowly injected followed by one-minute pauses and then repeated. When symptoms of warmth, face flush or headache occur, one should wait until they have disappeared before resuming the injection. This usually lasts a few minutes, when the speed can be controlled more slowly so as to avoid these reactions. The initial dose is doubled for the following day's injec-

tion and trebled for the third day's injection, although 1 mg. or more can be given on the third injection depending upon the rapidity of increased tolerance. Decreased itching and diminution in the size of the wheal may follow the first injection.

Alexander suggests a follow-up course of subcutaneous treatments pointing out that cases show a tendency to relapse within a few weeks if continual histamine administration is not maintained, and presents a schedule of dosage by the subcutaneous method in the treatment of chronic urticaria with histamine which is very satisfactory (H. L. Alexander, M.D., Synopsis of Allergy, St. Louis, C. V. Mosby Co., 1941). Briefly this consists of injections of increasing strengths of histamine diphosphate commencing with 0.05 c.c. of 1:10,000 dilution twice daily the first two days, and 0.1 c.c. the following two days followed by ten daily injections commencing with 0.15 c.c. and increasing 0.05 c.c. each day, when a 1:1000 dilution is used every two days commencing with 0.15 c.c. and increasing 0.05 with each succeeding dose for five injections, when a maintenance dose of 0.3 c.c. is injected every three days.

Shelden and Horton first suggested the use of the intravenous administration of histamine in treating Ménière's disease by giving 1.9 mg. of histamine acid phosphate (monophosphate) diluted with 250 c.c. of physiologic saline solution.

Previous sensitivity tests with histamine are an indicated preliminary procedure. The probable difference in opinion of the strength of histamine solutions to be used for sensitivity tests and therapeutic purposes is due to several factors: first, they are not standardized in terms of histamine base; second, a preliminary endermal test is not always done, and when performed the error is made of not adhering to a definite strength in solution in terms of the base. In arranging a dosage schedule, one must be guided by individual sensitiveness as well as the grade of allergic pathologic conditions, and must bear in mind the fact that histamine tolerance is increased very rapidly at the onset with close increasing doses. Solutions of histamine diphosphate and dihydrochloride are available in 1 c.c. ampules. Most of these ampules are in two strengths, the lowest dilution being 0.275 mg. of the acid or the diphosphate which represents 0.1 mg. of the base. The second dilution is ten times stronger. Ampules of dihydrochloride usually come in strengths of 1.5 mg. representing 0.1 mg. of the base. Therefore, to reduce the diphosphate, multiply the quantity of the former by 0.36; to reduce the dihydrochloride to the terms of histamine base, multiply by 0.66.

Most of the biologic houses market ampules of histamine acid phosphate in phenolized physiologic saline containing 0.275 mg. per c.c. (equivalent to histamine base 0.1 mg.). This is placed in 250 c.c. of physiologic saline and administered intravenously by the drip method very slowly (about 50 to 60 drops per minute). If there is flushing or headache, it is usually of comparatively short duration, and the administration briefly interrupted or continued slower. The next day the contents of two ampules containing 0.275 mg. of the acid phosphate may be given in the same manner, and on the third day the initial dose may be trebled. Usually satisfactory results are obtained by this time so that the subcutaneous method of administration can be commenced.

Thus solutions can be readily prepared of either salt in terms of base for endermal testing and subcutaneous testing. They can be made by diluting the contents of the ampules with sterile physiologic saline for the making of serial dilutions; however, it is much cheaper to buy the histamine in powdered form and dissolve it in phenolized (0.40) physiologic saline. The solutions, when possible, should be made in comparatively small amounts so that fresh solutions of the high dilutions can be made frequently (weekly), and always kept in a refrigerator (35-38 F). The higher the dilution, the more rapid the deterioration. At least a 1:1000 and a 1:10,000 dilution of histamine base should be available. A stronger 1:10 dilution which keeps its strength better can be used and diluted as required.

The solutions are passed through a Seitz filter and tested for sterility and all cloudy solutions discarded. They keep well in rubber capped sterile bottles. 0.4 per cent phenol is added. Some prefer histamine dihydrochloride as it can be purchased very cheaply in powdered form (Roche). However, be sure to dry out the powder if necessary on a warm plate before dissolving. When testing a patient's sensitivity to histamine the technique of Browne (J. Allergy, **14**:19, 1943) is suggested, using the volar surface of the forearm and lateral surface of the arm for endermic testing; he observed that the flare rather than the wheal was the better index, and a constant temperature environment (preferably 78° F. and 40 per cent humidity); he also preferred the supine position with the arm at a straight angle, observing the reactions from the light of a 75-watt Mazda lamp placed 2½ feet directly over the flare zone. He found that 1:100,000 dilution calculated as base (histamine acid phosphate used) was the most useful dilution of histamine for skin testing.

Under these conditions Browne found that histamine flares induced at intervals over a period of approximately two weeks and treated with gradually increasing amounts of histamine subcutaneously twice daily over the same period, lost their flares in 40 per cent of the cases; in 25 per cent the flares were significantly reduced, while in 35 per cent they were practically unchanged. There would thus seem to be a correlation between therapeutic results and the state of the histamine flare. Even if desensitization does show individual variation and is of comparatively short duration, it would be an aid in diagnosis and treatment. When such a system which is comparatively simple is used, it avoids the confusion of previous observers in attempting to evaluate skin sensitization without using standard procedures. So far, however, the dosage both subcutaneously and intravenously has been empirical. In the treament of Ménière's disease Horton found that two injections daily for ten to twenty-one days may be required; and if there is slight face flushing or other symptoms, the dose is reduced 50 per cent and gradually increased again. After cessation of attacks a preventive or maintenance dose of 1 c.c., one to three times a week, is sufficient. Some patients do not require a maintenance dose, and overdosing is to be avoided.

•

**I have two patients who are sensitive to Vitamin $B_1$, so much so that they cannot eat enriched foods (bread and cereals). Do you have any suggestions as to how these patients may tolerate Vitamin $B_1$?**

It has been found that some patients when taking Thiamine Chloride by mouth have a definite digestive upset and complain of belching or tasting the Thiamine Chloride after taking it by mouth. These same patients have been found to tolerate Thiamine Chloride in dosage up to 50 and 100 mgm. intravenously. It is desirable to give this preparation very slowly, dilute it in the beginning in 10 c.c. of normal saline; if no reaction is experienced from such dosage given in the above manner, it may be given as supplied in ampoules of the concentrated form without diluting it.

•

**Would you please give me a satisfactory procedure in the treatment of dermatophytosis and trichophytids?**

**M. D., Kansas**

In making a diagnosis of eczematous "ids" of the hands, it must be remembered that the lesions are characteristic of eczematous dermatitis whether in the nature of "ids" or other causes. Further, it may be impossible to differentiate between a dermatophytid and a staphyliid, streptococcid, moniliid or even an eczematous contact-type dermatitis. There is some unknown relationship between eczematous reactions on the hands and those on the feet and vice versa. Inability to demon-

strate fungi infection of the feet or other parts does not exclude the "id" nature of the lesion. The extent or duration of the foci also does not determine the production of "ids," although a trichophytid is the result of skin sensitization due to a primary lesion followed by an incubation period. This may be followed by malaise or even fever with other systemic signs and symptoms accompanied by glandular enlargements with the following of a hematogenous "id" eruption.

The skin between the toes may be very thin and pale with no demonstrable surface lesions. Several applications of full strength Whitfield's ointment will take off the superficial layer when mycelium or spores may be demonstrated. Local and immunologic (trichophytin) treatment should be started. Antiseptic ointments are less efficient than lotions in large foci of infection of the feet and toe nails. A potassium permanganate foot- or (hand-) bath (1:5000 for an antiseptic deodorant and antipruritic action is very satisfactory. Thus:

℞ Potassii permanganatis 1.50 Gm. (gr. xxiiss)
Aquæ destillatæ q.s. ad 30.00 c.c. (℥ i)

Paint lesions twice daily. May also be used as a foot-bath in solution of 1:5000. (Teaspoonful of solution to a quart of water.)

The feet should be soaked for at least one-half hour at bedtime, dried, and one-half strength Whitfield's ointment applied thoroughly between the toes and around the nails. This procedure is continued until the infection clears up.

Roentgentherapy is not generally required in the superficial forms. In the resistant cases (keratotic and verrucous types) fractional doses of x-ray therapy may be used. Care should be taken that all irritation from chemical irritants has subsided. Fractional doses of ¼ E.D. weekly for three or four weeks when erythema is avoided, sometimes give satisfactory results. Along with local treatment repeated endermal injections of trichophytin specifically reduces the skin sensitivity to the extract in many cases. For detailed description of the method of preparation of trichophytin refer to "Dermatologic Allergy" by Marion Sulzberger, M. D. (Charles C. Thomas, Pub.).

Trichophytin and oidiomycin derived from Monilia albicans are furnished by several biologic houses. The reactions from endermal testing with these extracts are quite similar to those of the tuberculin reaction and have a very limited diagnostic value. Repeated endermal injections of the specific extract usually specifically reduce the skin sensitivity to these extracts, and therapeutic results are varying but encouraging enough to warrant their use. They are undoubtedly beneficial in some cases of true trichophytids of the hands.

There is a close association in fungus diseases between the production of allergic sensitivity and immunity. The greater the skin sensitivity to trichophytin, the greater the tendency to spontaneous healing or favorable response to local and immunologic treatment. The fungous species which produce an immunologic response manifested by deep lesions, marked inflammatory changes and the scarcity of microorganisms respond more favorably to trichophytin and local treatment.

Dermatomycins, a proprietary extract, is a mixture of trichophytin and oidiomycin. The dosage is 0.1 c.c. intracutaneously every five to seven days; of trichophyton mixture one minim is given intracutaneously every seven days.

•

**Is rice flour frozen and is there any difficulty in procuring pure rye flour from the usual source of supply or from special health stores?**

On June 18 the OPA stated that none of the cereal grains were frozen. It is

very difficult to buy rice flour from any source at the present time, according to the Food Distribution Administration.

There is no definite scarcity of rye flour, so far as can be determined. One source of supply that might be considered is the Minneapolis Flour Company, 6000 Park Avenue, Cleveland, Ohio. This concern not only supplies the 100 per cent pure rye flour (aerated rye) but also rye meal which is the whole rye grain ground up, and this is much more satisfactory for making bread. A source of supply of 100 per cent rye meal bread is as follows: H. Schmidt, East 57th St. and Harvard, Cleveland, Ohio.

This bread will be mailed to patients having the need of 100 per cent rye bread containing absolutely no wheat, at a nominal charge.

White or yellow corn flour may be procured from the above source. There is a ceiling retail price on the corn flour of $3.70 per hundred, f. o. b. Cleveland, and the smallest amount that can be obtained from this source is 25 pounds. There is no ceiling at present on 100 per cent rice flour; the charge as of June 18 is $3.60 per hundred, f. o. b. Cleveland.

•

**Are canker sores an allergic condition?**

It has been found that many patients with allergy develop canker sores after eating certain foods. This type of canker sore may very well be termed as allergic; however, there is a second type of canker sore that occurs unaccompanied by any definite explanation or unassociated to any food that the patient has had in his diet—this type of canker sore has been explained on the basis of a virus infection. The allergic canker sores may be produced in one of the three following ways:

(1) The ingestion of food with the resulting canker sore from the digestion of the food.

(2) Following the ingestion of drugs.

(3) By contact. This last may result from contact with dental appliances and following the contact of certain foods to the tongue; for example, nuts; some patients may have canker sores within a few minutes after eating nuts.

•

**If a patient is allergic to sulfanilamide, is it practical to switch over to one of the other sulfonamides?**

Certain patients have been found to tolerate one sulfonamide preparation when another sulfonamide preparation causes symptoms either of conjunctivitis, gastro-intestinal distress, or skin eruptions. However, one has to take certain precautions, and the patient should be given a very small dose in the beginning in order to determine whether he is allergic to the second drug. A number of patients who have had difficulty with sulfathiazole, namely, gastro-intestinal distress, dizziness, headaches, have tolerated sulfadiazine without difficulty. The usual dosage of such drugs may vary from 2 to 4 grams in twenty-four hours. Many patients can take 2 grams of sulfadiazine or sulfathiazole over a period of three weeks and still be ambulatory without too much distress; however, the blood and urine and progress should be followed carefully during such a period.

•

**In the management of a case of atopic dermatitis, is it practical to consider hyposensitization?**

Hyposensitization should always be considered in any case of atopic dermatitis that does not respond to local treatment and dietary management.

# BIBLIOGRAPHY

These references represent the greater portion of material of interest to allergists which has appeared in the literature during the months of April, May and June, 1943.


Abramowitz, E. W.:
External use of 30 to 50 per cent sulfur in petrolatum in various dermatoses. New York State J. Med., **43:** 746, (May) 1943.

Albee, F. H.:
Preliminary report on the use of venom in arthritis. Med. Record, **156:** 217, (April) 1943.

Alimentone powder and tablets.
Thomas E. Collins Co., San Francisco, Shipped July 15, 1940. Tablets misbranded because directions for asthma victims were false and misleading. Bureau of Investigation. J.A.M.A., **122:** 394, (June 5) 1943.

Allergic tuberculosis immunity.
Current Comment, J.A.M.A., **122:** 310, (May 29) 1943.

Allergy to cocaine.
J.A.M.A., **121:** 1250, (April 10) 1943.

Allergy to iodine.
J.A.M.A., **121:** 1250, (April 10) 1943.

Allergy to liver extract. Letters, notes, et cetera.
Brit. M. J., **1:** 528, (April 24) 1943.

Altscheel, R.:
The effect of prostogmine and acetylcholine on denervated muscle. J. Nerv. & Ment. Dis., **97:** 549, (May) 1943.

Andrews, T. G.:
Statistical studies on allergy. 1. A correlation analysis. J. Allergy, **14:** 322, (May) 1943.

Applebaum, S., and Bachrach, E. H.:
Vesicular eruption following sulfathiazole intoxication. New York State J. Med., **43:** 870, (May) 1943.

Atkinson, M.: Ménière's syndrome and migraine; observations on a common causal relationship. Ann. Int. Med., **18:** 797, (May) 1943.

Barach, A. L.:
Repeated bronchial relaxation in the treatment of intractable asthma. J. Allergy, **14:** 296, (May) 1943.

Barrett, J. W.:
Hay fever. M. J. Australia, **1:** 339, (April 10) 1943.

Barton, R. L., and Brunsting, L. A.:
Kaposi's varicelliform eruption. Report of case. Proc. Staff Meet. Mayo Clin., **18:** 199, (June) 1943.

Batterman, R. C., and Himmelsbach, C. K.:
Demeral. A new synthetic analgesic. Its use in asthma. J.A.M.A., **122:** 224, (May 22) 1943.

Bernstein, F., Borison, H. L., and Finkel, S.:
A case of spurious linkage, as claimed for the classical blood groups and allergy. J. Immunol., **46:** 245, (April) 1943.

Biram, J. H.:
Prevention of skin rashes. The practical solution of the cutting oil problem. Indust. Med., **12:** 208. (April) 1943.

Black widow spider bites. Queries and Minor Notes.
J.A.M.A., **122:** 208, (May 15) 1943.

Blumstein, G. I.:
Sensitivity to ailanthus pollen. J. Allergy, **14:** 329, (May) 1943.

Boyer, N. H.:
Acute hemolytic anemia following sulfadiazine. New England J. Med., **228:** 566, (May 6) 1943.

Boyer, N. H.:
Aminophylline and related xanthine derivatives. (Asthma) p. 309. J.A.M.A., **122:** 306, (May 29) 1943.

## BIBLIOGRAPHY


Brown, E. A., and Goitein, P. L.:
The significance of body image for personality assay, with special application in allergy. J. Nerv. & Ment. Dis., **97**: 401, (April) 1943.

Brown, O. H.
Allergy studies in the tuberculous. Southwestern Med., **27**: 92, (April) 1943.

Brown, W. B., and Locke, A. P.:
Food allergy, its relation to common cold. J. Missouri M.A., **40**: 99, (April) 1943.

Cardinale, P. F.:
Possible late complications of anaphylactic reaction. J.A.M.A., **121**: 1185, (April 13) 1943.

Carletom, A.:
Skin disease and cataract. Allergic eczema. Brit. J. Dermat. & Syph., **55**: 83, (April) 1943.

Carson, M. J.:
Childhood allergy. Health Bull., **58**: 7, 1943.

Chemical fumes and allergy. Queries and minor notes.
J.A.M.A., **122**: 144, (May 8) 1943.

Chloracne "cable rash." Committee on Industrial Health.
Illinois M. J., **83**: 349, (May) 1943.

Chown, G.:
Allergic problems. Canad. M. A. J., **48**: 498, (June) 1943.

Chronic urticaria in prospective blood donor. Queries and minor notes.
J.A.M.A., **122**: 476, (June 5) 1943.

Clearkin, P. A.:
Hay fever in the tropics. Lancet, **1**: 509, (April 17) 1943.

Clusellas, F. J.:
Contribucion a la Terapéutica del Asma Bronquial po el Cobre Coloidaleléctrico Endoveroso. La Semana Medica, **50**: 816, (April 15) 1943.

Common problems in infancy. Types of allergy.
Roche Rev., **7**: 267, (May) 1943.

Criep, L. H.:
The importance of allergy in the practice of pediatrics. Pennsylvania M. J., **46**: 816, (May) 1943.

Criep, L. H.
Practice of allergy in the Veterans' Administration. M. Bull. Veterans' Adm., **19**: 414, (April) 1943.

Cruiskshank, A. G.:
Asthma in childhood. Brit. M. J., **1**: 550, (May 1) 1943.

Davis, H. J.:
Industrial dermatitis. Indust. Med., **12**: 381, (June) 1943.

Dean, G. A.:
Allergic rhinitis due to Spanish moss. J. Allergy, **14**: 340, (May) 1943.

Derbes, V. J., and Engelhardt, H. T.:
Incidence of bronchial asthma in the white and negro. Am. J. M. Sci., **205**: 675, (May) 1943.

Di Sant'Agnese, P., and Larkin, V. D.:
Vitamin A absorption in infantile eczema. Proc. Soc. Exp. Biol., **52**: 343, April) 1943.

Donovan, P. B., and Harsh, G. F.:
A comparison of the sodium and potassium metabolism of asthmatic and non-allergic children. J. Allergy, **14**: 281, (May) 1943.

Downing, J. G.:
Dermatitis in industry. Am. J. Nursing, **43**: 332, (April) 1943.

Dowling, H. F., and Lepper, M. H.:
Toxic reactions following therapy with sulfapyridine, sulfathiazole, and sulfadiazine. J.A.M.A., **121**: 1190, (April 10) 1943.

Dragstedt, C. A.:
The significance of histamine in anaphylaxis and allergy. Quart. Bull. N. U. Med. School, **17**: 102, 1943.

Drueck, C. J.:
Pruritus perinei in the aged. Proctology, **8**: 27, (April) 1943.

Edsall, G.:
Tetanus in the Middle East. J.A.M.A., **122**: 559, (June 11) 1943.

## BIBLIOGRAPHY


Elwell, G. H.
Febrile reactions accompanying sulfathiazole therapy. Jackson Clinic Bull., **5**: 85, (May) 1943.

Englehardt, H. T., and Derbes, V. J.:
Incidence of bronchial asthma in the white and negro. Am. J. M. Sci., **205**: 675, (May) 1943.

Eyermann, C. H.:
Inhalent allergy. J. Missouri M. A., **40**: 107, (April) 1943.

Fineman, A. H.:
Discussion of Dr. M. Weitz's paper: Hypersensitivity to insulin with desensitization. J. Allergy, **14**: 354, (May) 1943.

Fink, H. W., and Wilson, J. L.:
Evaluation of the dangers of repeated administration of sulfadiazine and sulfathiazole in children. J. Pediat., **22**: 513, (May) 1943.

Foerster, H. R., et al:
Recognition and prevention of industrial dermatitis with additional reference to oil dermatitis and folliculitis: a report of the Committee on Occupational Dermatoses, American Medical Association. J.A.M.A., **122**: 370, (June 5) 1943.

Fowler, E. P.:
Unilateral vasomotor rhinitis due to interference with the cervical sympathetic system. Arch. Oto-laryng., **37**: 710, (May) 1943.

Frank, D. E.:
Histaminase intramuscularly in hay fever. New York State J. Med., **43**: 339, (February) 1943.

Frank, D. E., and Gelfand, H. H.:
Studies on the blocking antibody in serum of ragweed-treated patients. A search for inhibiting substances in other types of immune serum. J. Allergy, **14**: 273, (May) 1943.

Friedman, A. J., and Cohen, A. E.:
Use of new ephedrine-like drug in hay fever and asthma. Northwest Med., **42**: 138, (May) 1943.

Fries, J. H., and Mogil, M.:
Roentgen observations on children with gastro-intestinal allergy to foods. J. Allergy, **14**: 310, (May) 1943.

Furstenberg, F. F., and Scherlis, S.:
Observations on the Weltmann reaction in hay fever and asthma. J. Allergy, **14**: 288, (May) 1943.

Gasoline dermatitis (Allergy). Bureau Legal Med. and Legislation. J.A.M.A., **122**: 57, (May 1) 1943.

Geer, E. K.:
Transient infiltration of the lung parenchyma associated with eosinophilia. Minnesota Med., **26**: 491, (May) 1943.

Goodman, M. H.:
Combined vaccine and toxoid therapy of staphylococci infections of the skin. Arch. Dermat. & Syphil., **47**: 640, (May) 1943.

Gordon, J.:
Acute tracheobronchitis complicated by bronchial stenosis following the inhalations of sulphur dioxide. New York State J. Med., **43**: 1054, (June 1) 1943.

Groh, R. H., and Veal, J. R.:
Cranial and abdominal migraine. Report of a case. Med. Ann., **12**: 147, (April) 1943.

Gottlieb, P. M., and Urbach, E.:
The distribution and pollinating times of the important hay fever-producing plants in the United States. J. Lab. & Clin. Med., **28**: 1053, (June) 1943.

Guy, W. H., and Jacob, F. M.:
Nail polish dermatitis. J.A.M.A., **122**: 571, (June 19) 1943.

Hansel, F. K.:
Allergy. Principals of diagnosis and treatment. J. Iowa M. Soc., **33**: 211, (May) 1943.

Hansel, F. K.:
Principles of diagnosis and treatment of allergy as related to oto-laryngology. Laryngoscope, **53**: 260, (April) 1943.

Heidelberger, M.:
Immunology as a tool in biological research. Immunochemical approach to biological problems. Am. Natur., **77**: 193, (June) 1943.

Helmick, J. P.:
Allergy to bubble bath. J.A.M.A., **121:** 1250, (April 10) 1943.
Hennig, H. V.:
Reactivity of the skin effect of anesthesia and shock on the histamine and allergic responses. U. S. Nav. M. Bull., **41:** 698, (May) 1943.
Honey for infant feeding. Queries and minor notes.
J.A.M.A., **122:** 268, (May 22) 1943.
Horesh, A. J.:
Allergy to food odors; its relation to the management of infantile eczema. J. Allergy, **14:** 333, (May) 1943.
Hunt, E. L.:
Death from allergic shock. New England J. Med., **228:** 502, (April) 1943.
Hurst, A.:
Asthma in childhood. Brit. M. J., **1:** 403, (April 3) 1943.
Jacox, R. F., and Hurd, R. W.:
Thrombopenic purpura developing as a complication of sulfathiazole and sulfadiadine therapy. J.A.M.A., **122:** 296, (May 29) 1943.
Jameson, W. L.:
Mineralaid. Shipped Mar. 17, 1941. Misbranded because falsely represented to give the user health, afford relief in cases of hay fever, asthma, sinus trouble. Bureau of Investigation. J.A.M.A., **122:** 394, (June 5) 1943.
Kadisch, E. L.:
Contact dermatitis caused by dyes in wearing apparel. New York State J. Med., **43:** 1051, (June 1) 1943.
Karnosh, L. J., and Zucker, E. M.:
Horse serum neuritis. Ohio State M. J., **39:** 416, (May) 1943.
Kato, K., Sherman, M. S., and Cannon, P. R.:
Fatal agranulocytosis following sulfathiazole therapy. J. Pediat., **22:** 431, (April) 1943.
Kelly, E. F.:
Acne from synthetic wax (Halowax). Urol. & Cut. Rev., **47:** 238, (April) 1943.
King, E., and King, J. H.:
Symptomatic and empiric treatment of the allergic nose. Arch. Otolaryng., **37:** 645, (May) 1943.
Klaften, E.:
Contribution to the treatment of essential pruritus and kraurosis vulvae. J. Clin. Endocrinol., **3:** 218, (April) 1943.
Knox, J. S.:
Histamine and insulin in erythematous eczema. Brit. M. J., **1:** 426, (April 3) 1943.
Kobernick, S. D.:
The etiology of rheumatic fever. (Experiments on allergic manifestations, p. 64.) McGill M. J., **12:** 56, 1943.
Kracke, R. R., and Townsend, E. W.:
The effect of sulfonamide drugs on the blood platelets. J.A.M.A., **122:** 168, (May 15) 1943.
Kuhn, H. A.:
Relationship of allergy to hearing defects. J. Indiana M. A., **36:** 143, 1943. Abstracted in: Therapeutic Notes. May-June, p. 162, 1943.
Lambert, E., and Rosenthal, S. R.:
Study of skin histamine with some results of splanchnic nerve stimulation. Proc. Soc. Exp. Biol. & Med., **52:** 302, (April) 1943.
Lindley, W. H.
(DVM): Theory of nonspecific canine dermatitis. North Am. Vet., **24:** 365, (June) 1943.
MacGregor, I. M.:
Dermatitis after local sulphanilamide treatment of a wound. Brit. M. J., **1:** 414, (April 3) 1943.
Mackenzie, G. W.:
Sensitization diagnosis—desensitization treatment (four different methods). J. Am. Inst. Homeo., **36:** 123, (April) 1943.
Madden, J. F.:
Reaction due to sulfapyridine in the treatment of dermatitis herpetiformis. Arch. Dermat. & Syphil., **47:** 695, (May) 1943.

Manning, I. H., Jr., and Milan, D. F.:
Medical and nutritional survey of 800 N.Y.A. youths. South. M. J., **36:** 373, (May) 1943.

Mantoux test versus patch test.
Medical Memoranda. Brit. M. J., **1:** 603, (May 15) 1943.

Manwaring, W. H.:
Complexity of serum complement. California & West. Med., **58:** 218, (April) 1943.

Markuson, K. E., Manciso, T. F., and Soet, J. S.:
Dermatitis due to the formaldehyde resins. Indust. Med., **12:** 383, (June) 1943.

Mason, R. W., Jr., and Swineford, O.:
Passive autosensitization and desensitization. South. M. J., **36:** 324, (May) 1943.

Mease, J. A.:
Deer fly desensitization, J.A.M.A., **122:** 227, (May 22) 1943.

Melton, G.:
Treatment of asthma by nicotinic acid. Brit. M. J., **1:** 600, (May 15) 1943.

Melvin, R. G.:
Dr. Johnson's asthma. Brit. M. J., **1:** 584, (May 8) 1943.

Miscall, L., and Rovenstine, E. A.: Physiologic basis for the surgical treatment of asthma. Surgery, **13:** 495, (April) 1943.

Mohun, M.:
Incidence of vasomotor rhinitis during pregnancy. Allergy p. 709. Arch. Otolaryngol., **37:** 699, (May) 1943.

More help for milk allergic patients. Trade News Section.
Wisconsin M. J., **42:** 638 (June) 1943. Also: Tuberculosis Absts., **40:** 33, (July 19) 1943.

Nielson, J. M.:
Bromidism after excessive dosage of prostigmine bromide for myasthenia gravis. J.A.M.A., **122:** 496, (June 19) 1943.

O'Brien, C. S., and Allen, J. H.:
Allergic kerato-conjunctivitis. Arch. Ophth., **29:** 600, (April) 1943.

O'Donnell, M. C.:
Toxic reactions of paredrine-sulfathiazole suspension: report of two cases. J.A.M.A., **122:** 298, (May 29) 1943.

O'Donovan, D. K.:
Sulphonamides in asthma. Brit. M. J., **1:** 551, (May 1) 1943.

Oral desensitization to dust. Queries and minor notes.
J.A.M.A., **122:** 208, (May 15) 1943.

Osgood, H.:
Blood pressure fluctuation in bronchial asthma. 1. Clinical observations. J. Lab. & Clin. Med., **28:** 927, (May) 1943.

Pascher, F., Sulzberger, M. B., and Satenstein, D. L.:
Histologic studies of reactions to intracutaneous tests in allergy of infection in humans. J. Immunol., **46:** 195, (April) 1943.

Pelner, L.:
Histadine—histamine antagonism; the possible mode of action of histadine in peptic ulcer. Rev. Gastroenterol., **10:** 108, (April) 1943.

Pelner, L.:
The treatment of periodic occipital headache with desensitizing doses of prostigmin. Dis. Nerv. System, **4:** 177, (June) 1943.

Peshkin, M. M.:
Immunity to tetanus induced by a third dose of toxoid two years after basic immunization based on a study of 31 allergic children. Am. J. Dis. Child., **65:** 873, (June) 1943.

Peshkin, M. M., Rapaport, H. G., Meser, W., Feuer, I., Sicular, A., and Berger, A.:
Histaminase in the treatment of allergy in children. J. Pediat. **22:** 426, (April) 1943.

Peterson, W. F.:
Influence of weather changes on otolaryngological diseases. Trans. Am. Acad. Ophthal. & Otolaryngol., (May-June) 1943.

Phenyton sodium for asthma. Queries and minor notes. J.A.M.A., **121:** 1316, (April 17) 1943.

Pinto, S. S., Brown, R. A., and Carlton, B. H.:
Study of industrial workers exposed to sulfur dust. J. Indust. Hyg. & Toxicity, **25:** 149, (April) 1943.

Rambar, A. C., Lt. Comm., Howell, K. M., and Denenholz, E. J., Capt.:
Studies in immunity to pertussis. Am. J. Dis. Child., **65:** 730, (May) 1943.

Ratner, B.:
Allergy, Anaphylaxis, and Immuno-therapy. Baltimore: Williams & Wilkins, 1943.

Rehfuss, M. E.:
Indigestion: Its Diagnosis and Management. (Allergy, 152-157.) Phila.: W. B. Saunders Co., 1943.

Reiman, H. A., Price, A. H., and Herbert, P. A.: Trichinosis and periarteritis nodosa: differential diagnosis; possible relationship. J.A.M.A., **122:** 296, (May 29) 1943.

Rhodes, W. L.
Allergy and infection of the nose and paranasal sinuses. Record, **156:** 224, (April) 1943.

Rogerson, C. H.:
Psychological factors in asthma. Brit. M. J., **1:** 406, (April 3) 1943.

Ronchese, F.:
Dermatitis vaccinia (Kaposi's varicelliform eruption). Arch. Dermat. & Syphil., **47:** 613, (May) 1943.

Rosenow, E. C.:
Streptococcic antibody antigen reactions of the serum and skin of monkeys during attacks of experimenal poliomyelitis. Proc. Staff Meet. Mayo Clin., **18:** 205, (June) 1943.

Satulsky, E. M., Capt., and Wirts, C. A., Major:
Dermatitis venenata caused by the manzanillo tree. Arch. Dermat., **47:** 797, (June) 1943.

Satulsky, E. M. and Halper, W.:
Dermatitis venenata caused by phenol-camphor mixtures. J. M. Soc. New Jersey, **40:** 137, (April) 1943.

Saunders, T. S.:
Personal experiences in treatment of commoner dermatoses. Northwest Med., **42:** 135, (May) 1943.

Schlenker, L.:
Allergy from chemical fumes. J.A.M.A., **122:** 144, (May 8) 1943.

Schwartz, L.:
Contact dermatitis due to resin-finished facing in cotton underwear. Arch. Dermat. & Syphil., **47:** 697, (May) 1943.

Schwartz, L.:
An outbreak of dermatitis from airplane engine covers. U. S. Pub. Health Rpts., **58:** 625, (April 16) 1943.

Schwartz, L.:
Problems of proof in claims for recovery for dermatitis. Ann. Int. Med., **18:** 500, (April) 1943.

Schwartz, L.:
An outbreak of halowax acne ("cable rash") among electricians. J.A.M.A., **122:** 158, (May 15) 1943.

Scott, H. C.:
Toxic reactions to sulphathiazole. Brit. M. J., **1:** 635, (May 22) 1943.

Scott, R. A. M.:
Reactions to ephedrine. Brit. M. J., **1:** 414, (April) 1943.

Seegers, W. H.:
A convenient arrangement for rapid dialysis. J. Lab. & Clin. Med., **28:** 897, (April) 1943.

Seidmann, M.:
Cutaneous eruptions due to codeine. Arch. Dermat. & Syph., **47:** 654, (May) 1943.

Sensitivity to milk and cheese—butter and oleomargarine. Queries and minor notes. J.A.M.A., **122:** 410, (June 5) 1943.

Shambaugh, G. E.:
Nasal allergy. J. Michigan M. S., **42:** 441, (June) 1943.

Siegal, M., Randall, M. G., et al:
Study on the value of a mixed bacterial oral cold vaccine. Am. J. M. Sci., **205:** 687, (May) 1943.

## BIBLIOGRAPHY


Smith, H. D., Goodhull, V., and Webb, M. E.:
Nasal allergy: the otolaryngologists' problem in relation to Southern California districts. California & West. Med., **58:** 275, (May) 1943.

Sprague, C. H.:
The incidence of pulmonary tuberculosis in bronchial asthma. Connecticut M. J., **7:** 399, (June) 1943.

Stehle, R. L., and Melville, K. I:
The action of adrenaline upon the atropine-acetyl choline reversal phenomenon. J. Pharmacol. & Exper. Therap., **77:** 332, (April) 1943.

Strohmenger, W. L.:
Generalized eczematoid dermatitis, angioneurotic edema and anuria from sulfathiazole. U. S. Nav. Med. Bull., **41:** 825, (May) 1943.

Sutton, R. L., Jr.:
Contact dermatitis from olive oil. J.A.M.A., **122:** 34, (May 1) 1943

Swartz, J. H., and Lever, W. F.:
Dermatitis herpetiformis; immunologic and therapeutic considerations. Arch. Derm. Syph., **47:** 680, (May) 1943.

Thomas, J.:
Active immunization against tetanus. Nebraska M. J., **28:** 150, (May) 1943.

Thomas, J. W.:
Bronchial asthma following the inhalation of powdered neoarsphenamine; attempted oral hyposensitization. Arch. Derm. Syph., **47:** 675, (May) 1943.

Torda, C.:
Effect of chloroform and ether on the sensitivity of muscle to acetylcholine. J. Pharmacol. & Exper. Therap., **77:** 350, (April) 1943.

Treatment of tetanus. Exposed patient previously immunized with toxoid. Queries and minor notes. J.A.M.A., **122:** 571, (June 19) 1943.

Trowbridge, L. S., Cushman, D., Gray, M. G., and Moore, M.:
Notes on the personality of patients with migraine. J. Nerv. & Ment. Dis., **97:** 509, (May) 1943.

Turnbull, J. A.: Allergy as a factor in thrombosis. Am. J. Digest Dis., **10:** 184, (May) 1943.

Turnbull, J. A.
The tired, weak, exhausted, depressed patient. Am. J. Digest. Dis., **10:** 218, (June) 1943.

Urbach, E., and Gottlieb, P. M.:
Allergy. New York: Grune & Stratton, 1943.

Vaughan, Warren T.:
On contact dermatitis. South. M. J., **36:** 380, (May) 1943.

Vaughan, W. T.:
On lacquer dermatitis. Virginia M. Monthly, **70:** 193, (April) 1943

Vaughan, Warren Taylor:
Primer of allergy; a guidebook for those who must find their way through the mazes of this strange and tantalizing state. (Illustrations by John P. Tillery.) 2nd ed. 176 p. illus. diagrs. 20 cm. St. Louis: The C. V. Mosby Company, 1943.

Vollmer, H., and Ripps, M. L.:
Pseudoreactions to tuberculin. Am. J. Dis. Child., **65:** 763, (May) 1943.

Waldbott, G. L.:
Hay fever treatment during the season. Tri-State M. J., **15:** 2949, (May) 1943.

Warren, L. H.:
Patch tests; their practical applications and limitations. South. M. J., **36:** 434, (June) 1943.

Watkins, A. L.:
Infra-red urticaria. Arch. Phys. Therapy, **24:** 291, (May) 1943.

Weingarten, R. J.:
Tropical eosinophilia. Lancet, **1:** 103 (June 23) 1943.

Werner, H. W., Mitchell, J. L., Miller, J. W., and von Oettingen, F.:
The acute toxicity of vapors of several monoalkyl ethers of ethylene glycol. J. Indust. Hyg. & Toxicol., **25:** 157, (April) 1943.

Workmen's Compensation Acts:
A mere allergic condition not compensable. Medicolegal abstracts, Bur. of Legal Med. and Legislation. J.A.M.A., **122:** 57, (May) 1943.

# BOOK REVIEWS

*Books listed here become the property of the College library when reviewed. A micro film or miniature photostat service will be available to the members at cost. Members, however, are requested to write reviews on any book which may be of interest to allergists.*

FAMILIAL NONREAGING FOOD-ALLERY. By Arthur F. Coca, M.D., 160 pages, 20 tables, 12 charts. Price, $3.00. Springfield: Charles C. Thomas, 1943.

In this monograph Coca makes a new method of diagnostic approach to a relatively large group of allergic diseases (migraine, urticara, gastro-intestinal allergy, nuralgia and a number of more or less serious syndromes hitherto unrecognized as allergic) in which the usual skin tests almost completely fail. The author states that the method provides a practical and accurate means of recognizing the offenders of food-allergy, so that one can determine at last which symptoms and symptom-complexes are food-allergic. He explains the theoretical approach and technical evidence with his usual clear and precise manner, emphasizing the necessity of careful attention to details when making the tests. All allergists recognize Doctor Coca as one of the early outstanding pioneers in allergy and especially for his definition and concept of atopy, a category of allergic disease subject to a common hereditary cause, and distinguishable from hypersensitiveness of infection, serum-disease and contact dermatitis. He explains that this new category although controlled by hereditary influence is independent of atopic inheritance; allergic antibodies ("reagins") are not demonstrable and many of the symptoms differ from the atopic group. The most important observation clinically is that the allergic reaction in this group practically always causes acceleration of the pulse.

The term "familial nonreaginic allergy" would also be proper since the excitants may be drugs, metals, or inhaled fumes or dusts. Skin tests usually fail and the customary trial diets give very unsatisfactory results in this new group. The author reports in detail his observations of forty-four cases, and gives explicit instructions for the practical management of these cases including a trial diet and histamine therapy. He presents a statistical method of approach to determine whether a certain syndrome is a symptom of nonreaginic food-allergy.

There is a preliminary report on the relation of familial nonreaginic food-allergy to hypertension as well as evidence offered of the importance of food-allergy as a predisposing cause of common cold.

The practical value of the new procedure will depend upon the confirmation of these observations by competent allergists who are open minded and who realize the general failure of cutaneous tests and the unsatisfactory results of the usual trial diets in most cases of nonreaginic food-allergy.

F.W.W.

---

CLINICAL IMMUNOLOGY, BIOTHERAPY AND CHEMOTHERAPY IN THE DIAGNOSIS, PREVENTION AND TREATMENT OF DISEASE. By John A. Kohlmer, M.S., M.D., Ph.D., Sc.D., K.L.D., F.A.C.P., and Louis Tuft, M.D. 941 pages. Illus. Price, $10.00. Philadelphia: W. B. Saunders Co., 1941.

This book is truly a complete clinical application of immunologic procedures correlated with biotherapy and chemotherapy. Clearly stated detailed methods for the administration of sera, vaccines and antitoxins as well as management of their

reactions are given. It contains the essential information for the use of the sulfonamides. Detailed technique of the various tests with their interpretation make it comparatively simple for the practitioner.

There is a complete presentation of the subject of blood transfusion and blood storage. The book reflects in every chapter the extensive experiences of the authors in this most important field of medicine, and unessential details and theories are climinated. Graphic tables serve to summarize the chapters in an exceptionally clear manner.

F.W.W.

---

ALLERGY, ANAPHYLAXIS, AND IMMUNOTHERAPY. Basic Principles and Practice. By Bret Ratner, M.D. 809 pages. Illustrated. Price, $8.50. Baltimore: The Williams and Wilkins Company, 1943.

Ratner's desire was to write a comprehensive treatise on the fundamental principles and practice governing the use of antisera, vaccines, toxoids, blood transfusions, blood substitutes and sulfonamides in the prevention and treatment of infectious diseases. This goal is fully achieved. The author presents to the practitioner an authoritative guide on modern immunotherapy on 360 pages. The second part of the book discusses allergy to immunotherapeutic agents with particular emphasis on serum disease and its complications. The third section is devoted to anaphylaxis and the physiological pathology of the more important allergic phenomena.

The physician, as well as the student of immunology, will find this treatise concise, practical and at the same time thought provoking.

E.U.

---

ALLERGY. By Erich Urbach, M.D., with the collaboration of Philip M. Gottlieb, M.D. 1100 pages. 400 illustrations; 80 tables and charts. Price, $12.00. New York: Grune & Stratton, Inc., 1943.

The author, a writer and teacher of international prominence, presents a comprehensive treatise on one of the most important fields of medicine. The book includes a basic critical analysis of the accumulated scientific research on allergy, as well as a practical application of these principles by modern clinical and technical methods.

There are three divisions of the text. Part I deals with the fundamentals of hypersensitiveness and the principles of diagnosis and treatment. Part II discusses the entire range of offenders responsible for allergic diseases. Part III extensively deals with symptomatology, diagnosis and therapy including the author's classification based on the newer concepts of allergy.

Four hundred illustrations and eighty tables and charts are invaluable aids in differential diagnosis, and present at the same time a most welcome visual survey of the clinical manifestations and testing methods in every type of allergic condition. Nine full-page graphic pollination calendars are another feature of the book.

The author reviews a vast literature with innumerable citations covering the entire field of previous literature on the subject, at the same time expressing his own views as to clinical methods and procedures. The value of this becomes immediately apparent when one considers the author's reputation in the fields of research and practice over a quarter of a century. The book is well bound, has good type and paper, and the pictures carry a real meaning to the reader.

F.W.W.

PRIMER OF ALLERGY. Second edition. By Warren T. Vaughan, M.D. 176 pages. 26 illustrations. Fabrikoid. Price, $1.75. St. Louis: C. V. Mosby Co., 1943.

The appearance of a second edition in a comparatively short time of this handy little guide book for the victim of allergy is evidence of its popularity with both the physician and the patient.

The author of two outstanding textbooks on allergy, "Practice of Allergy" and "Allergy and Applied Immunology" by the same publishers, has condensed into a bedtime story form invaluable information for the relief of those suffering from the various and puzzling symptoms of the allergic state. This book, somewhat like the author's first book of similar nature, "Strange Malady" (Doubleday, Doran and Co.), is widely serviceable in easy instruction of the patient so that he may not only coöperate with his doctor but the latter may learn of a simple approach of imparting sound, practical advice to the patient.

The primer is replete with graphic A-B-C descriptions and drawings illustrating the fundamental principles of the present-day acceptance of the mechanism of allergy.

Since food sensitization is the commonest allergic manifestation, either as a primary or secondary factor in disturbing the allergic equilibrium, the author stresses specific directions to the patient concerning the management of this difficult situation by means of elimination diets, symptom and food charts, etc. Directions also are explicit to the patient for the coöperative management of his inhalant allergies. There are questions and answers about those problems most likely to be puzzling to the patient.

Much time is spared the busy doctor when explaining the puzzling details of this strange sickness to his patients by the use of this handy primer.

F.W.W.

---

## COLLEGE NEWS

*(Continued from Page 66)*

The College now has two hundred Fellows, not including Associate or Honorary Fellows, and applications are being received daily.

The Honorary Fellows are Dr. Arthur F. Coca, Pearl River, N. Y.; Col. S. W. French, M.C., Chief, Medical Branch, Hdqrs. Fourth Service Command, Atlanta, Georgia; Prof. Wm. F. Petersen, Chief, Department of Bacteriology and Pathology, University of Chicago; and Prof. E. C. Stakman, Chief, Division of Plant Pathology and Botany, Department of Agriculture, University of Minnesota.

One-third of the Fellows are in the United States military service. A number of them are assigned to allergy stations and are receiving an invaluable experience. Measures have been taken for those devoting services to their various specialties to receive credits when applying for examination by their specialty boards.

The central laboratory for the making of standardized allergenic extracts for use by members of the College on a coöperative basis is under the direction of Dr. B. G. Efron of New Orleans. Doctor Efron has been working hard on these extracts since March. In order to make purified, standardized extracts on a large scale, however, considerable additional equipment, material and reagents will be required. No priorities have been obtained, and an experienced personnel is very difficult to establish at this time. The work is progressing satisfactorily considering these handicaps, but extracts will not be available for several months and then will be limited to a few of the most important ones. When available, due notice will be published in THE ANNALS.

The Fellowship Certificates will be framed and forwarded within the next four weeks, together with a booklet containing a copy of the Constitution and By-Laws. These will be sent to the home address of those in the Service.

Encouraging progress is being made with the Research Foundation. In carrying out one of its research problems, the College has been fortunate in securing the services of an expert medical reference librarian for the compiling of a comprehensive compendium-type bibliography and abstracts on all subjects pertaining to allergy from the earliest times, and will be available to Fellows of the College on a cost basis.

# ALLERGENS

## *for the busy Allergist*

AN independent laboratory, as a source of supply for diagnostic and desensitization material, is doubly appreciated in these days of increased practice and reduced technical assistance.

Hollister-Stier Laboratories are pioneers and exclusive specialists in the preparation of such material . . . making available over 200 pollen extracts . . . up to 400 protein extracts . . . and autogenous extracts of all types. All are approved by the A. M. A.'s Council on Pharmacy and Chemistry, and licensed by the National Health Institute—and are promptly available through laboratories in Pennsylvania, Washington and California.

It is particularly noteworthy—that Hollister-Stier allergens are true extracts and are prepared by the preferred glycerine-saline method of extraction . . . packaged in bulk vials. They are fresh, potent, and stable—second to none by every recognized standard of quality—and economically priced.

Send for full details. Address nearest laboratory, Dept. W-2.

ACCEPTED AMERICAN MEDICAL ASSN.

**HOLLISTER-STIER LABORATORIES**

Wilkinsburg, Pa.
Los Angeles, Calif.
Spokane, Wash.



Barry OFFERS THE *Complete* ALLERGY SERVICE

CONVENIENT LOCATION permits prompt and efficient service on all allergy materials.

Highly concentrated extracts, accurately standardized at reasonable prices.

**FUNGI**
**EPIDERMALS**
**POLLENS**
**FOODS, ETC.,**

for TREATMENT or TESTING purposes.

Write for detailed descriptive literature AA-7.

*Service to the medical profession for more than a decade*

*Barry Allergy Laboratories, Inc.*
9100 Kercheval at Holcomb, DETROIT, MICH.



**Buy**

**War Bonds**

**and**

**Stamps**